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PENICILLIN IN THE TREATMENT OF EXPERIMENTAL SYPHILIS OF RABBITS

I. The Therapeutic Activity of Penicillin in Single and Multiple Doses in Isotonic Solution of Sodium Chloride and Peanut Oil–Beeswax by Intramuscular Injection

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PHILADELPHIA

STUDIES bearing on penicillin in the treatment of experimental syphilis of rabbits are of value in relation to the treatment of human syphilis, as has been found true of the organic arsenical and bismuth compounds. Not only are the clinical effects of the compound on acute testicular and cutaneous lesions and on spirochetes in these lesions readily observed by means of dark field examinations, but dosage in relation to complete or biologic cure may be determined with a fair degree of accuracy by means of transfer of lymph nodes.

PRINCIPLES INVOLVED

It is true that the total dosage of penicillin per kilogram of weight required for the biologic cure of acute testicular syphilis of rabbits is much less than that required for the treatment of early syphilis of human beings. However, valuable information may be gained in relation to methods of administration, the relative therapeutic effectiveness of penicillins F, G, X and K and similar factors. Thus Mahoney, Arnold and Harris,[1] who first discovered the activity of penicillin against Treponema pallidum in the treatment of experimental syphilis of rabbits, stated that their early results indicated that the time-dose relationship would have an important bearing on penicillin therapy, and this observation has been amply confirmed. All investigators in the United States have apparently used the same Nichols-Hough strain of T. pallidum, with the result that this factor has been held constant, although the time elapsing between

From the Research Institute of Cutaneous Medicine.

1. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis, Am. J. Pub. Health **33**:1387 (Dec.) 1943.

inoculation of the testicles and the institution of treatment has varied, as, likewise, the time elapsing after the cessation of treatment before transfers of lymph nodes were made and the period of observation thereafter in relation to complete or biologic cure as well.

Indeed, the time-dosage factor has such an important influence on the total dosage per kilogram of weight required for the biologic cure of rabbits that it is difficult to correlate the results observed by different investigators. For example, Raiziss [2] has reported that 1 rabbit given two doses of 2,500 units each in aqueous solution per kilogram twice daily for eight days in succession (40,000 units) showed biologic cure, as, likewise, 1 rabbit given 3,300 units in aqueous solution per kilogram three times a day for eight days in succession (79,200 units). Incidentally, Raiziss also observed that penicillin administered intramuscularly in peanut oil to 4 rabbits was somewhat more effective than intramuscular injections of the compound in aqueous solutions, an observation which has been amply confirmed by our experiments herewith reported. Ercoli and Lafferty,[3] on the other hand, have reported that total doses as high as 132,000 to 282,000 units of sodium penicillin per kilogram, divided into four to six intravenous injections, were insufficient for complete biologic cure of rabbits on the basis of transfer of lymph nodes, while Eagle, Magnuson and Fleischman [4] stated that 10,000 units in aqueous solution by intramuscular injection per kilogram twice daily for four days (80,000 units) cured 90 per cent of rabbits, as, likewise, 400 units per kilogram given five times daily for four days (8,000 units). Furthermore, it is highly probable that the results reported have been greatly influenced by the amounts of penicillins G and X present in the sodium salts of penicillin employed with special reference to penicillin G.

METHODS AND MATERIALS

In our experiments all rabbits were inoculated intratesticularly with the Nichols-Hough strain of T. pallidum. Acute orchitis developed in all, with strongly positive results on dark field examinations about five to six weeks thereafter, when treatment was instituted. Dark field examinations were then made once a day for three days in succession and thereafter once a week over a total period of seventy days. At the expiration of this period the popliteal lymph nodes of all treated animals were inoculated into the testicles of fresh animals, which were kept under observation for a minimum of four months, when the results were evaluated.

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2. Raiziss, G. W.: Penicillin in Oil Suspension: Bacteriostatic and Spirochetal Agent, Science **100**:412 (Nov. 3) 1944; The Effect of Penicillin in Experimental Rabbit Syphilis, ibid. **102**:329 (Sept. 28) 1945.

3. Ercoli, N., and Lafferty, L. C.: The Anti-Spirochetal Activity of Penicillin in Experimental Infections, Proc. Soc. Exper. Biol. & Med. **57**:4 (Oct.) 1944.

4. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, J. Ven. Dis. Inform. **27**:3 (Jan.) 1946.

The penicillins employed in treatment were amorphous sodium salts supplied by the Commercial Solvents Corporation. One was a commercial product (no. 45072102) with an assay potency of 544 units per milligram, containing 88 per cent penicillin G;[5] in the tables it is referred to as "commercial" penicillin. The second (no. 45072104) was a purified product with an assay potency of 1,624 units per milligram, containing 92 per cent penicillin G;[5] in the tables it is referred to as "purified" penicillin.

Aqueous solutions of both lots were freshly prepared as required in sterile isotonic solution of sodium chloride containing 10,000 units per cubic centimeter. Suspensions were also prepared in sterile peanut oil and 3 per cent beeswax containing 10,000 units per cubic centimeter; these were kept at 4 C.

All doses were given in terms of units per kilogram of weight by intramuscular injection in the thighs, followed by brief massage.

RESULTS OBSERVED

Single Doses in Isotonic Solution of Sodium Chloride.—As shown in table 1, rabbits were given single intramuscular injections of the commercial and purified penicillins in doses of 10,000, 30,000 and 100,000 units per kilogram, 2 rabbits being treated with each dose respectively. It will be noted that negative results on dark field examinations occurred in about seventy-two hours after each dose, followed by relapsing infections, with positive results from transfers of lymph nodes in every instance. So far as temporarily negative results from dark field examinations are concerned, it will be observed that these effects were more pronounced with the purified than with the commercial penicillin. The single minimal curative dose in isotonic solution of sodium chloride of both penicillins, however, was not determined except to state that it was more than 100,000 units per kilogram of weight.

Single Doses in Peanut Oil and Beeswax.—As shown in table 2, however, the results were much different when similar doses were administered in peanut oil and 3 per cent beeswax. In this experiment a single dose of 10,000 units of the commercial penicillin per kilogram effected the biologic cure of both rabbits and in 1 of 2 animals treated with the purified penicillin. All rabbits treated with single doses of 30,000 and 100,000 units of both penicillins showed biologic cure, so that in these experiments the single minimal curative dose of penicillin in peanut oil and beeswax was approximately 10,000 units per kilogram of weight.

Multiple Doses in Isotonic Solution of Sodium Chloride.—As shown in table 3, both penicillins in isotonic solution of sodium chloride were administered intramuscularly once daily for eight days in succession in doses of 1,000, 5,000 and 25,000 units per kilogram, totaling 8,000, 40,000 and 200,000 units respectively. All 4 animals receiving a total of 8,000 units per kilogram showed temporarily negative results on dark

5. Smith, L. W.: Personal communication to the authors.

TABLE 1.—*Single Doses of Commercial and Purified Penicillins in Isotonic Solution of Sodium Chloride by Intramuscular Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

No.	Penicillins	Dose, Units per Kg.	Results of Dark Field Examination for T. Pallidum, Days *													Results of Transfer of Lymph Nodes
			1	2	3	7	14	21	28	35	42	49	56	63	70	
1	Commercial	10,000	2	1	1	—	4	4	4	4	4	4	4	4	4	Positive
2	Commercial	10,000	2	1	—	—	2	4	4	4	4	4	4	4	4	Positive
3	Commercial	30,000	2	1	—	—	4	4	4	4	4	4	4	4	4	Positive
4	Commercial	30,000	2	1	1	—	3	4	4	4	4	4	4	4	4	Positive
5	Commercial	100,000	2	1	—	—	—	—	—	3	4	4	4	4	4	Positive
6	Commercial	100,000	2	1	—	—	—	—	—	4	4	4	4	4	4	Positive
7	Purified	10,000	4	1	1	—	—	—	—	1	4	4	4	4	4	Positive
8	Purified	10,000	3	1	—	—	—	—	—	1	4	4	4	4	4	Positive
9	Purified	30,000	2	1	—	—	—	—	—	2	4	4	4	4	4	Positive
10	Purified	30,000	2	1	1	—	—	—	—	3	4	4	4	4	4	Positive
11	Purified	100,000	2	1	—	—	—	—	—	2	2	4	4	4	4	Positive
12	Purified	100,000	2	1	—	—	—	—	—	3	4	4	4	4	4	Positive

* After treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

TABLE 2.—*Single Doses of Commercial and Purified Penicillin in Peanut Oil and Beeswax by Intramuscular Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

No.	Penicillins	Dose, Units per Kg.	Results of Dark Field Examination for T. Pallidum, Days *													Results of Transfer of Lymph Nodes
			1	2	3	7	14	21	28	35	42	49	56	63	70	
1	Commercial	10,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
2	Commercial	10,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
3	Commercial	30,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
4	Commercial	30,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
5	Commercial	100,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
6	Commercial	100,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	Purified	10,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Positive
8	Purified	10,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
9	Purified	30,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
10	Purified	30,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
11	Purified	100,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
12	Purified	100,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative

* After treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

field examinations, but all relapsed, with positive results on transfer of lymph nodes. Both animals given a total of 40,000 units of commercial penicillin showed persistently negative results on dark field examinations but positive results on transfer of lymph nodes; both animals given 40,000 units of purified penicillin likewise showed persistently negative results on dark field examinations, but 1 showed a negative result on transfer of a lymph gland. All 4 animals given 200,000 units showed persistently negative results on dark field examinations and negative results on transfer of lymph nodes. In the circumstances the minimal curative dose of penicillin in these experiments by intramuscular injection once a day for eight days in succession was in the neighborhood of 5,000 units per dose, totaling 40,000 units per kilogram of weight.

Much different results, however, were observed when the same doses were given twice daily for eight days in succession, as shown in table 4. In this experiment both rabbits given 1,000 units of commercial penicillin per kilogram (totaling 16,000 units) showed biologic cure, with similar results observed in 1 of 2 rabbits given purified penicillin. All 4 animals given a total of 80,000 units and all 4 given a total of 400,000 units per kilogram also showed biologic cure. In these experiments, therefore, the minimal curative dose of penicillin by intramuscular injection twice daily for eight days in succession was approximately 1,000 units per kilogram, totaling 16,000 units.

Multiple Doses in Peanut Oil and Beeswax.—As in the case of single doses, however, much better therapeutic results were observed when both penicillins were administered in the same multiple doses suspended in peanut oil and 3 per cent beeswax. Thus, as shown in table 5, the effects on results of dark field examinations were more pronounced. Furthermore, both rabbits given 1,000 units of commercial penicillin per kilogram once a day for eight days in succession (8,000 units) showed biologic cure, with a similar result in 1 of 2 rabbits given purified penicillin. All 4 rabbits given a total dosage of 40,000 units per kilogram also showed biologic cure, and the same results were observed in all 4 given a total dosage of 200,000 units per kilogram. In the circumstances the minimal curative dose of penicillin by intramuscular injection in peanut oil and beeswax once a day for eight days in succession was approximately 1,000 units per kilogram, totaling 8,000 units.

In a second experiment the same doses were given intramuscularly twice daily for eight days in succession, totaling 16,000, 80,000 and 400,000 units per kilogram respectively. As shown in table 6, all animals showed persistently negative results on dark field examinations after the first two to three days of treatment and all yielded negative results on transfer of lymph nodes. In the circumstances the minimal curative dose of penicillin in peanut oil and beeswax by intramuscular injection twice daily for eight days in succession was less than 1,000 units, totaling less than 16,000 units, per kilogram of weight.

TABLE 3.—*Multiple Doses of Commercial and Purified Penicillins in Isotonic Solution of Sodium Chloride by Intramuscular Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

No.	Penicillins	Dose,* Units per Kg.	Total Dosage, Units per Kg.	Results of Dark Field Examination for T. Pallidum, Days †													Results of Transfer of Lymph Nodes
				1	2	3	7	14	21	28	35	42	49	56	63	70	
1	Commercial.....	1,000	8,000	2	1	1	—	—	—	—	—	4	4	4	4	4	Positive
2	Commercial.....	1,000	8,000	2	2	1	—	—	—	—	2	4	4	4	4	4	Positive
3	Commercial.....	5,000	40,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Positive
4	Commercial.....	5,000	40,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Positive
5	Commercial.....	25,000	200,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
6	Commercial.....	25,000	200,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	Purified.....	1,000	8,000	2	1	1	—	—	—	—	—	—	—	4	4	4	Positive
8	Purified.....	1,000	8,000	2	1	1	—	—	—	—	—	—	2	4	4	4	Positive
9	Purified.....	5,000	40,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Positive
10	Purified.....	5,000	40,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
11	Purified.....	25,000	200,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
12	Purified.....	25,000	200,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative

* Once daily for eight days in succession.

† After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field examination; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results in dark field examinations.

TABLE 4.—*Multiple Doses of Commercial and Purified Penicillins in Isotonic Solution of Sodium Chloride by Intramuscular Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

No.	Penicillins	Dose,* Units per Kg.	Total Dosage, Units per Kg.	Results of Dark Field Examination for T. Pallidum, Days †													Results of Transfer of Lymph Nodes
				1	2	3	7	14	21	28	35	42	49	56	63	70	
1	Commercial.....	1,000	16,000	4	1	1	—	—	—	—	—	—	—	—	—	—	Negative
2	Commercial.....	1,000	16,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
3	Commercial.....	5,000	80,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
4	Commercial.....	5,000	80,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
5	Commercial.....	25,000	400,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
6	Commercial.....	25,000	400,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	Purified.....	1,000	16,000	4	1	1	—	—	—	—	—	—	—	—	—	—	Positive
8	Purified.....	1,000	16,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
9	Purified.....	5,000	80,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
10	Purified.....	5,000	80,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
11	Purified.....	25,000	400,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
12	Purified.....	25,000	400,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative

* Twice daily for eight days in succession.

† After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field examination; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results in dark field examinations.

TABLE 5.—*Multiple Doses of Commercial and Purified Penicillins in Peanut Oil and Beeswax by Intramuscular Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

No.	Penicillins	Dose,* Units per Kg.	Total Dosage, Units per Kg.	Results of Dark Field Examination for T. Pallidum, Days †													Results of Transfer of Lymph Nodes
				1	2	3	7	14	21	28	35	42	49	56	63	70	
1	Commercial.....	1,000	8,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
2	Commercial.....	1,000	8,000	2	2	1	—	—	—	—	—	—	—	—	—	—	Negative
3	Commercial.....	5,000	40,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
4	Commercial.....	5,000	40,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
5	Commercial.....	25,000	200,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
6	Commercial.....	25,000	200,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	Purified.....	1,000	8,000	4	1	1	—	—	—	—	—	—	2	2	3	3	Positive
8	Purified.....	1,000	8,000	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative
9	Purified.....	5,000	40,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
10	Purified.....	5,000	40,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
11	Purified.....	25,000	200,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
12	Purified.....	25,000	200,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative

* Once daily for eight days in succession.
† After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field examination; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results in dark field examinations.

TABLE 6.—*Multiple Doses of Commercial and Purified Penicillins in Peanut Oil and Beeswax by Intramuscular Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

No.	Penicillins	Dose,* Units per Kg.	Total Dosage, Units per Kg.	Results of Dark Field Examination for T. Pallidum, Days †													Results of Transfer of Lymph Nodes
				1	2	3	7	14	21	28	35	42	49	56	63	70	
1	Commercial.....	1,000	16,000	4	1	1	—	—	—	—	—	—	—	—	—	—	Negative
2	Commercial.....	1,000	16,000	4	1	1	—	—	—	—	—	—	—	—	—	—	Negative
3	Commercial.....	5,000	80,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
4	Commercial.....	5,000	80,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
5	Commercial.....	25,000	400,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
6	Commercial.....	25,000	400,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	Purified.....	1,000	16,000	4	2	1	—	—	—	—	—	—	—	—	—	—	Negative
8	Purified.....	1,000	16,000	4	1	1	—	—	—	—	—	—	—	—	—	—	Negative
9	Purified.....	5,000	80,000	2	2	1	—	—	—	—	—	—	—	—	—	—	Negative
10	Purified.....	5,000	80,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
11	Purified.....	25,000	400,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
12	Purified.....	25,000	400,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative

* Twice daily for eight days in succession.
† After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field examination; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results in dark field examinations.

SUMMARY

1. In the treatment of acute syphilitic orchitis of rabbits the minimal single curative dose of commercial and purified amorphous sodium salts of penicillin in isotonic solution of sodium chloride by intramuscular injection was more than 100,000 units per kilogram of weight.

2. The single minimum curative dose of the penicillins suspended in sterile peanut oil and beeswax by intramuscular injection, however, was approximately 10,000 units per kilogram of weight.

3. The minimal curative dose of the penicillins in isotonic solution of sodium chloride given intramuscularly once a day for eight days in succession was approximately 5,000 units per dose per kilogram, totaling 40,000 units.

4. The minimal curative dose of the penicillins in isotonic solution of sodium chloride given intramuscularly twice daily for eight days in succession was approximately 1,000 units per dose per kilogram, totaling 16,000 units.

5. The minimal curative dose of the penicillins suspended in sterile peanut oil and beeswax by intramuscular injection once a day for eight days in succession was approximately 1,000 units per dose per kilogram, totaling 8,000 units.

6. The minimal curative dose of the penicillins suspended in sterile peanut oil and beeswax by intramuscular injection twice daily for eight days in succession was less than 1,000 units per dose per kilogram, or less than a total of 16,000 units.

7. Penicillin suspended in peanut oil and beeswax by intramuscular injection, therefore, was found to be therapeutically more effective in the treatment of acute syphilitic orchitis of rabbits than that administered dissolved in isotonic solution of sodium chloride by intramuscular injection.

8. The commercial penicillin employed contained approximately 88 per cent penicillin G and the purified penicillin approximately 92 per cent penicillin G.

9. So far as these experiments are concerned the results observed with commercial and purified lots of sodium penicillin were closely similar.

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ACANTHOSIS NIGRICANS JUVENILIS ASSOCIATED WITH OBESITY

Report of a Case, with Observations on Endocrine Dysfunction in Benign Acanthosis Nigricans

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ACANTHOSIS nigricans has been a disease of interest to dermatologists and internists since it was first independently described in 1890 by Pollitzer [1] and Janovsky.[2] Reports of about 400 cases of acanthosis nigricans have appeared to date in the medical literature.[3] The conditions in these cases have been divided almost equally into the adult type, occurring in persons after the age of 20 years, which is usually associated with intra-abdominal malignant growth, and the juvenile benign type, occurring in persons under 20 years of age, without evidence of internal malignant growth. According to Curth,[3c] however, no strict dividing line in age is possible between the so-called malignant and benign forms of acanthosis nigricans, as in some of the cases of the juvenile type either an internal malignant growth has developed while the patient was under 20 years of age or an internal malignant growth has appeared later in adult life. In the majority of the cases reported, the condition has been associated with no internal pathologic changes, and the cause of the disease is considered to be unknown. Numerous hypotheses and theories concerning the cause of juvenile and benign acanthosis nigricans have been advanced by investigators since the earliest reports have appeared. Pollitzer [1] considered the cause to be due to intra-abdominal

From the Department of Dermatology of the University of Southern California School of Medicine.

1. Pollitzer, S., in Internationaler Atlas von seltener Hautkrankheiten, Leipzig, Leopold Voss, 1890, plate 10.

2. Janovsky, V., in Internationaler Atlas von seltener Hautkrankheiten, Leipzig, Leopold Voss, 1890, plate 11.

3. (*a*) Moncorps, C.: Acanthosis Nigricans, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankeiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, p. 372. Bibliography of papers on acanthosis nigricans published before 1931. (*b*) Michy, J.: L'acanthosis nigricans et ses rapports avec les tumeurs malignes, in Monographies sur les tumeurs, Laboratoire du Professeur Peyron, Institut Pasteur, Paris, E. Le François, 1932, no. 12. (*c*) Curth, H. O.: Cancer Associated with Acanthosis Nigricans, Arch. Surg. **47**:517 (Dec.) 1943.

fibrous bands, adhesions and congenital malformations. Janovsky [2] advanced the theory of excessive exposure to heat. Porias [4] suggested that the dystrophies of the skin depend on the altered secretion of internal glands and dysfunction of chromaffin tissue. Oppenheim and Loeper [5] expressed the opinion that dysfunction or disease of the suprarenal glands was an etiologic factor in acanthosis nigricans. Other hypotheses advanced as to the cause of benign acanthosis nigricans have been exposure to cold,[2] syphilis,[6] decapsulation of the kidneys,[7] hepatic cirrhosis [8] and injury or disturbance to the abdominal sympathetic nervous system.[9]

It is of interest that no article has appeared in the American dermatologic or medical literature on juvenile acanthosis nigricans associated with obesity. The findings of endocrine dysfunction involved in the reported case and in other cases of the juvenile type associated with obesity compiled from the medical literature reveal observations that may be of aid to advance further the knowledge concerning the cause of the benign form of this disease. It is the purpose of this paper to report a case of acanthosis nigricans juvenilis associated with obesity, to present a compilation of cases of this type from the reports in the medical literature and to discuss the dysfunction of the endocrine gland associated with the benign type of this disease.

REPORT OF A CASE

History.—M. P., a 17 year old school boy, was examined because of a pigmented eruption on the neck, axillas and crurogenital area of three years' duration. Similar lesions had recently appeared on the forehead, chest, back and hands. No subjective symptoms were associated with the eruption. During the preceding few months the pigmented areas had darkened, roughened and slowly spread. No other members of his family suffer from cutaneous disease. The patient has been obese since early childhood. His weight at birth was 5 pounds 7 ounces (2,477 Gm.). At 5 years of age he was 20 pounds (9.09 Kg.) overweight, short in stature and had "stubby" fat hands. At 7 years he weighed 88½ pounds (41 Kg.) and his height was 50 inches (127 cm.). A roentgenogram of both wrists at the age of 7 years showed retarded epiphysial development, and a diagnosis of Fröhlich's syndrome was made by an endocrinologist. Intensive endocrine therapy with posterior pituitary injection and two proprietary preparations of chorionic gonadotropin was administered from April 1935 to June 1937,

4. Porias, J.: Ueber die Beziehungen der Akanthosis nigricans zu malignen Tumoren, Wien. klin. Rundschau **27**:671, 1913.

5. Oppenheim, R., and Loeper, M.: L'insuffisance surrénale experimentale par lésions directes des capsules, Compt. rend. Soc. de biol. **55**:332, 1903.

6. de Azua, J.: Acanthosis Nigricans, J. Cutan. Dis. **31**:966, 1913.

7. Wise, F.: Acanthosis Nigricans Following Decapsulation of the Kidneys, J. Cutan. Dis. **36**:35, 1918.

8. Crocker, cited by Moncorps.[3a]

9. (*a*) Wile, U., in discussion on Wieder.[18] (*b*) Masson, J. C., and Montgomery, H.: Relationship of Acanthosis Nigricans to Abdominal Malignancy, Am. J. Obst. & Gynec. **32**:717, 1936.

without retarding the patient's progressive obesity. At the age of 8 years his weight was 111 pounds (53 Kg.) and his height was 51½ inches (130.8 cm.). At the age of 9 years his weight was 130 pounds (59 Kg.) and his height was 55 inches (139.7 cm.). The patient's present weight is 315 pounds (143.2 Kg.), and his height is 5 feet 9 inches (175.2 cm.). His mental development has been normal, and he is of average intelligence. His father is obese, and his mother suffers from pituitary type of obesity. One brother, aged 15 years, is obese and weighs 200 pounds (91 Kg.).

Physical Examination.—The patient was a well developed obese young man who appeared to be of stated age. The hair was normal in distribution and texture.

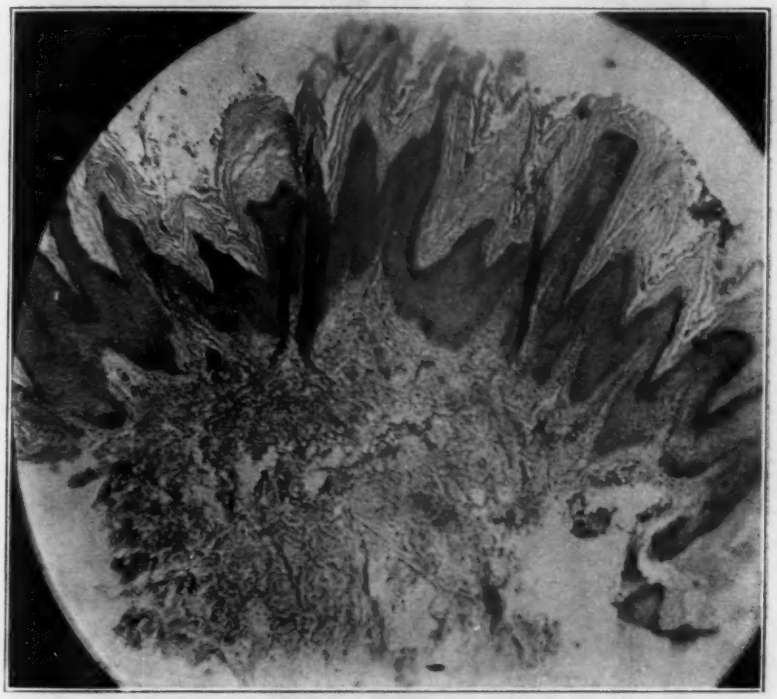

Fig. 1.—Acanthosis nigricans, juvenile type. Photomicrograph (low power) of section of skin from the axilla, showng hyperkeratosis, acanthosis, increased pigment granules in basal cell layer and decided papillary hypertrophy.

The obesity was especially located in the abdominal region, with an apron-like pendulous distribution. The hands were short and stubby, with shortened thick fingers. The finger nails were irregular and discolored and broken off in their distal portions. The genitals showed normal development. The heart, lungs and nervous system were normal. The examination of the abdomen showed no masses or areas of tenderness. The spleen and liver were not palpable. The blood pressure was 160 systolic and 86 diastolic.

Dermatologic Examination.—A diffuse brownish black hyperkeratotic plaque-like papular eruption was located on the forehead, neck, axillas, upper part of the chest, lower part of the back, dorsa of the hands and genitocrural regions. The

skin of the axillas and inguinal regions was thickened and furrowed. Numerous small discrete elevated brownish verrucae and papules were superimposed on the pigmented axillary patches. Some of these papillomas were pedunculated. On the chest and back were numerous discrete, superficial, brownish, macular, scaling lesions. Superimposed on the pigmented furrowed skin of the left groin and extending to the lower part of the abdomen was an annular palm-sized lesion with a papulovesicular scaling raised border and a clear center. The lips, tongue and oral mucous membranes were normal.

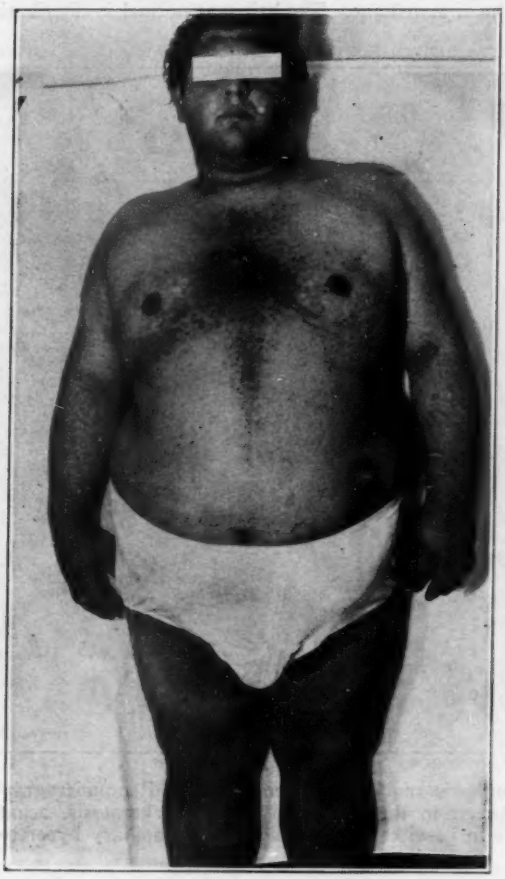

Fig. 2.—Acanthosis nigricans, juvenile type, associated with obesity.

Laboratory Examinations.—The Wassermann and Kahn tests of the blood elicited negative serologic reactions for syphilis. Examination of the blood showed a hemoglobin content of 82 per cent, a color index of 0.9, 4,600,000 erythrocytes and 6,800 leukocytes with 77 per cent neutrophils, 17 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. The dextrose tolerance test by the two dose method of Exton and Rose gave results as follows: fasting specimen, 89 mg. per hundred cubic centimeters; one-half hour after ingestion of the first dose (50

Gm.) of dextrose, 130 mg., and one-half hour after ingestion of the second dose (50 Gm.) of dextrose, 112 mg. The examination of the blood plasma for ascorbic acid showed 0.4 mg. per hundred cubic centimeters, compared with the normal value of 0.8 to 2.4 mg. The result of a basal metabolic test was plus 8 per cent. The urine was normal. Roentgenograms of the skull showed the sella turcica to be normal in size and shape, with normal clinoid processes.

Histologic Examination.—A biopsy specimen from the right axilla was stained with hematoxylin and eosin. The epidermis showed relative and absolute

Fig. 3.—Acanthosis nigricans, juvenile type, showing involvement of the lateral surface of the neck.

hyperkeratosis with irregular acanthosis and adjacent areas of atrophy of the rete cell layer. The papillary bodies were elongated and narrow. The basal layer of the epidermis contained considerable melanin pigment. Examination of the cutis showed occasional chromatophores laden with melanin pigment. No inflammatory reaction or disturbance of the connective tissue could be found in the corium. The blood vessels and subcutaneous fat tissue were normal. The microscopic diagnosis was acanthosis nigricans.

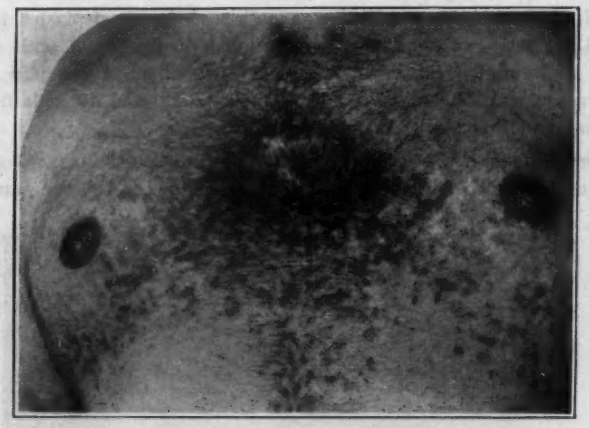

Fig. 4.—Acanthosis nigricans, juvenile type, showing involvement of the chest. The lesions of tinea versicolor are superimposed on the pigmented patches of acanthosis nigricans.

Fig. 5.—Acanthosis nigricans, juvenile type, showing axillary involvement with papillomas.

Microscopic examination of scrapings from the superficial macular lesions of the back and chest revealed Microsporon furfur. Scrapings from the elevated border of the annular lesion on the groin examined microscopically revealed myceliums and spores of dermatophytosis. Scrapings from the nails were negative for fungi on microscopic examination and culture.

The clinical and laboratory diagnosis was juvenile acanthosis nigricans associated with obesity of endocrine type, tinea versicolor of the trunk and dermatophytosis involving the crural and abdominal regions.

Treatment.—The patient was given a restricted diet, and a salicylic acid exfoliating cream was prescribed for the pigmented areas. Because of the low level of ascorbic acid in the blood, ascorbic acid in high dosage was administered orally and intramuscularly. No beneficial effects were noted in the cutaneous picture as a result of this therapy. The tinea versicolor on the trunk and the

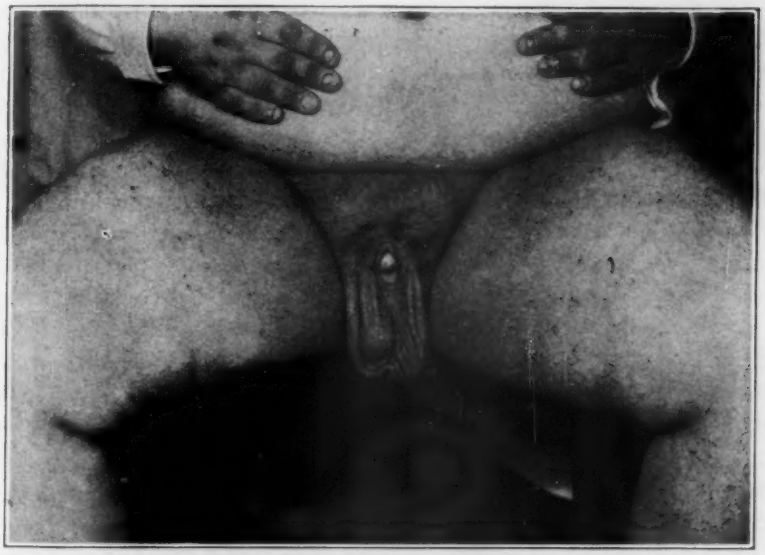

Fig. 6.—Acanthosis nigricans, juvenile type, showing increased pigmentation and hyperkeratosis about the crurogenital region. The pigmented patches on the dorsa of the hands and the dyskeratotic finger nails can be seen.

dermatophytosis in the groin were treated with a fungicidal ointment. The mycotic infections cleared readily, but there was no gross change in the underlying patches of acanthosis nigricans.

COMMENT

The cause of the adult type of acanthosis nigricans has been accepted by most investigators [10] to be due to an internal malignant growth affecting the suprarenal glands and chromaffin system. The malignant growth in almost all cases has been intra-abdominal in origin and commonly originates in the stomach. Malignant growths associated with acanthosis nigricans that occur primarily outside of the abdominal cavity include

10. Curth.[3c] Wile.[9a]

those having origin in the breast [11] and lungs.[12] Regardless of its origin, the malignant growth commonly metastasizes to the splanchnic region of the abdomen, especially the suprarenals. The cause of the juvenile or benign form of acanthosis nigricans has been obscure. Most of the recorded cases of benign conditions have had no mention of associated internal pathologic changes or abnormal metabolism. A compilation was made of reports of cases of benign acanthosis nigricans associated with dysfunction of the endocrine gland (table 1). Examination of this compilation shows dysfunction of the endocrine gland to be a common finding associated with the benign type of this disease when internal pathologic or metabolic disorders are found. Among the ductless glands reported [3a, c] to have disturbances associated with benign acanthosis nigricans are the thyroid, thymus, chromaffin system, pituitary body, pancreas, suprarenals and gonads. No single type of dysfunction of the endocrine gland has been found consistently in benign forms of the condition. This lack of association of a single definite type of disturbance of the endocrine gland has led Curth [13] and Grace and Schwartz [14] to oppose the belief that endocrine dysfunction is an etiologic basis for the disease. In support of their belief, Grace and Schwartz pointed out that no endocrine disturbance is known to produce cutaneous changes similar to those found in acanthosis nigricans and that organotherapy is of no value in benign forms or others. Knowles, Sidlick and Ludy [15] likewise did not consider disease or functional disturbance of the suprarenal glands in itself to be responsible for the cutaneous picture of acanthosis nigricans. Among investigators who considered benign acanthosis nigricans to be due to endocrine dysfunction are Hellerstrom,[16] Smith [17] and Wieder.[18] Hellerstrom stated the belief that the endocrine character of benign acanthosis nigricans is demonstrated by its retrogression after castration in a patient who also suffers from severe diabetes mellitus. Smith's patient with benign acanthosis nigricans also suffered from acromegalic gigantism, a dis-

11. Curth.[3c] Masson and Montgomery.[9b]

12. Cited by Curth.[3c]

13. Curth, H. O.: Benign Type of Acanthosis Nigricans: Etiology, Arch. Dermat. & Syph. **34**:353 (Sept.) 1936; footnote 3*c*.

14. Grace, A. W., and Schwartz, H. J.: Acanthosis Nigricans: Case of Benign Form in Adult Investigated from Aspect of Endocrine Dysfunction, Arch. Dermat. & Syph. **29**:691 (May) 1934.

15. Knowles, F. S.; Sidlick, D. M., and Ludy, J. B.: Acanthosis Nigricans. Arch. Dermat. & Syph. **19**:391 (March) 1929.

16. Hellerstrom, S.: Zur Kenntnis der Acanthosis nigricans, Acta dermat.-venereol. **14**:86, 1933.

17. Smith, S. W.: A Case of Juvenile Acanthosis Nigricans, Brit. J. Dermat. **45**:142, 1933.

18. Wieder, L. M.: Acanthosis Nigricans, Juvenile Type, J. A. M. A. **87**:1964 (Dec. 11) 1926.

TABLE 1.—*Reports of Benign Acanthosis Nigricans Associated with Dysfunction of the Endocrine Gland*

Authors	Disease	Bibliography
Kemeri, D.	Hypothyroidism and dwarfism in 5 members of a family	Orvosi hetil. **81**: 329, 1937
Patrassi, G.	Hypothyroid syndrome, Buschke's scleroderma and hyperlipemia of diencephalic origin following psychic trauma	Riv. di pat. nerv. **50**: 148, 1937
Presented by the Mayo Clinic	Hyperthyroidism and exophthalmic goiter	Arch. Dermat. & Syph. **22**: 163, 1930
Knowles, F. C., and Ludy, J. B.	Hyperthyroidism; basal metabolic rate, minus 15 per cent	Presented at the Atlantic Derm. Conf., Dec. 2, 1927 (Arch. Dermat. & Syph. **17**: 746, 1928)
Behjet, H.	Dysfunction of the thyroid gland (goiter)	Dermat. Wchnschr. **99**: 934, 1934
Masson, J. C., and Montgomery, H. (cases 1, 9 and 10)	Adenoma of thyroid gland (goiter)	Am. J. Obst. & Gynec. **32**: 717, 1936
Perman, B. (case 3)	Dysfunction of the thyroid gland (goiter)	Acta med. Scandinav. **70**: 30, 1929
Flaskamp, W.	Dysfunction of the thyroid gland	Deutsche med. Wchnschr. **50**: 1180, 1924
Miescher, G.	2 cases of congenital familial acanthosis nigricans associated with diabetes mellitus	Dermat. Ztschr. **32**: 276, 1921
Milian, G. J.	Diabetes mellitus	Medicina, México **21**: 123, 1941
Ravogli, A.	Diabetes mellitus	Cited by Wise, F.: J. Cutan. Dis. **36**: 35, 1918
Hermans, E. H., and Schokking, C. R.	Diabetes mellitus	Nederl. tijdschr. v. geneesk. **84**: 4965, 1940
Pollitzer, S.	Diabetes mellitus	J. A. M. A. **53**: 1369, 1909
Lawrence, R. D.	Diabetes mellitus (hemochromatosis)	Proc. Roy. Soc. Med. **34**: 556, 1941
Hellerstrom, S.	Severe diabetes mellitus (familial)	Acta dermat.-venereol. **14**: 86, 1933
Weiss, A.	Crypto-orchism	Klin. Monatsbl. f. Augenh. **78**: 190, 1927
Ottkhine, A. T.	Double crypto-orchism	Ann. de dermat. et syph. **6**: 650, 1926
Goldschlag	Pluriglandular insufficiency	Zentralbl. f. Haut- u. Geschlechtskr. **55**: 339, 1937
Barenblat, J.	Pluriglandular insufficiency: infantilism, small sella turcica, crypto-orchism, persistent thymus in an 18 year old youth	Med.-biol. j. **4**: 50, 1928
Artom, M.	Facies hypopituitaria (2 cases)	Gior. ital. di dermat. e sif. **69**: 184, 1928
Smith, S. W.	Acromegalic gigantism; pituitary and suprarenal dysfunction	Brit. J. Dermat. **45**: 142, 1933
Welder, L. M.	Hypofunction of suprarenal glands and increased sugar tolerance	J. A. M. A. **87**: 1964, 1926

ordered abdominal sympathetic system and probable suprarenal cortical disease. This investigator considered benign acanthosis nigricans to be a combined disease with origin in the endocrine glands affecting the pituitary body, suprarenal glands and the abdominal sympathetic system. In support of his belief, Smith stated that anterior pituitary secretion plus excess suprarenal function is known to occur in the adrenal cortex in both gigantism and acromegaly. Wieder expressed the opinion that hypofunction of suprarenal glands increases tolerance for sugar, because in his case acanthosis nigricans was associated with impairment of secretion of the ductless glands, particularly the suprarenals. Curth,[13] although stating that there is no basis for assuming an endocrine causation in the benign type of the disease, expressed the belief that the common onset and spread of acanthosis nigricans in and through puberty is evidence in favor that "sex hormones play some role in the propagation of the disease." We are in agreement with the foregoing findings and opinions of investigators favoring the relationship of dysfunction of the endocrine glands to benign acanthosis nigricans. We believe that such findings and opinions tend to strengthen one's thoughts that endocrine dysfunction may play an important role in the cause of the benign type of this disease.

A review of the literature revealed the reports of 10 cases of acanthosis nigricans juvenilis associated with obesity (table 2). The geographic distribution of the cases was in Europe, North America and South America. All patients in the group were in the age of puberty, and all except 1 were females. Our patient is the second male patient to be recorded. In some of the cases reported the patients with obesity had a history of familial obesity or familial acanthosis nigricans associated with obesity (table 2; cases 1*a* and 1*b*). Our patient likewise had a familial history of obesity. Roentgenograms of the sella turcica have been normal in all cases when reported. Becker and Obermayer (table 2; case 8) recorded that their patient showed a decreased tolerance for dextrose and hypertension on exertion. Our patient likewise was found to have hypertension. Senear's patient (table 2; case 9) suffered from mild hypothyroidism. All other patients in the series had a normal basal metabolic rate when reported and showed no evidence of thyroid dysfunction. Butterworth (table 2; case 7) reported that his obese patient lost weight when given a restricted diet and thyroid extract, with no resultant gross change in the cutaneous picture. Senear and Cornbleet (table 2; case 3) conversely reported that their patient lost 30 pounds (13.6 Kg.) by restricted diet, with resultant almost complete involution of the pigmented patches. Two of the 9 females in the series suffered from amenorrhea and dysmenorrhea, but there were no definite findings of ovarian dysfunction. The obesity reported in almost all instances was of pituitary type due to insufficiency of the anterior lobe. The age of onset of obesity, when reported, was in early childhood. The obesity

TABLE 2.—*Reported Cases of Acanthosis Nigricans Juvenilis Associated with Obesity*

Case No.	Age	Sex	Weight and Height	Laboratory Findings (Diagnosis Proved by Histologic Section in Each Case)	Comment	Bibliography
1 a.	14	♀	193.6 lb. (88 Kg.)	Results of sugar tolerance tests normal for both patients	Familial acanthosis nigricans associated with obesity in a mother, daughter and son	Jadassohn, W.: Arch. f. Dermat. u. Syph. **150** 110, 1926
b.	11	♂	143 lb. (65 Kg.)			
2	16	♀	184¼ lb. (83.6 Kg.); 5 ft. 1½ in. (156.27 cm.)	None reported	Endocrine dysfunction present	Presented by Dr. Wertheimer at the meeting of the Pittsburgh Dermatological Society, June 21, 1928 (Arch. Dermat. & Syph. **19**: 162, 1929)
3	17	♀	280 lb. (127 Kg.)	Basal metabolic rate minus 10 per cent	Jewish woman with acanthosis nigricans of 2 yr. duration; onset of corpulency at age 9; dysmenorrhea; reduced 30 lb. (13.6 Kg.) by restricted diet in 2 mo. with resultant almost complete involution of pigmented acanthosis nigricans patches	Presented by Dr. F. E. Senear and Dr. T. Cornbleet at the meeting of the Chicago Dermatological Society, Oct. 17, 1928 (Arch. Dermat. & Syph. **19**: 511, 1929)
4	12	♀	260 lb. (117.9 Kg.)	Roentgenogram of sella turcica normal	Negro woman suffering from endocrine dysfunction	Presented by Dr. Rapp and Dr. Klauder at the meeting of the Philadelphia Dermatological Society, Dec. 3, 1938 (Arch. Dermat. & Syph. **19**: 323, 1929)
5	17	♀	225 lb. (102 Kg.); 5 ft. 6 in. (167.6 cm.)	Basal metabolic rate plus 10; roentgenogram of sella turcica normal	Endocrine type in appearance; no history of ovarian dysfunction	Presented by Dr. H. E. Michelson at the meeting of the Minneapolis Dermatological Society, Oct. 23, 1930 (Arch. Dermat. & Syph. **23**: 388, 1931)
6	15	♀	207 lb. (94 Kg.); 5 ft. 4½ in. (164 cm.)	Roentgenogram of sella turcica normal	Scanty menses every 3 or 4 mo.	Presented by Dr. A. Sayer at the meeting of the Bronx Dermatological Society, Nov. 30, 1936 (Arch. Dermat. & Syph. **36**: 448, 1937)
7	16	♀	231 lb. (104.8 Kg.)	Basal metabolic rate normal	Obesity considered to be of pituitary type; patient lost 12 lb. (5.4 Kg.) in 5 wk. when placed on restricted diet and 2 grains (0.13 Gm.) of thyroid extract daily; there was no gross change in the cutaneous picture	Butterworth, T.: Arch. Dermat. & Syph. **39**: 552, 1939
8	11	♀	236 lb. (106.6 Kg.)	Reaction to tuberculin test negative; basal metabolic rate normal; decreased tolerance for dextrose	Patient gained 40 lb. (18 Kg.) in 3 yr.; obesity had distribution of the pituitary habitus; hypertension on exertion; mild diabetes mellitus	Presented by Dr. S. W. Becker and Dr. M. E. Obermayer at the meeting of the Chicago Dermatological Society, May 21, 1941 (Arch. Dermat. & Syph. **45**: 235, 1942)
9	15	♀	187 lb. (85 Kg.)	Wassermann reaction of the blood positive; roentgenogram of sella turcica normal	Mild hypothyroidism of 3 yr. duration	Presented by Dr. F. E. Senear at the meeting of the Chicago Dermatological Society, May 21, 1941 (Arch. Dermat. & Syph. **45**: 236, 1942)
10	11	♀	169 lb. (77 Kg.)	Basal metabolic rate normal; roentgenogram of sella turcica normal	Fröhlich syndrome type of obesity; familial obesity; acanthosis nigricans of 2 mo. duration	Garzon, R., and Sagues, P. L.: Rev. argent. dermatosif. **26**: 1030, 1942

was of progressive type and usually antedated the acanthosis nigricans by years. The diagnosis made for our patient at the age of 7 was Fröhlich's syndrome, and the acanthosis nigricans appeared when he was 14 years old. The pituitary type of obesity associated with juvenile acanthosis nigricans in most cases in our series would tend to support the belief that endocrine disturbance involving the pituitary gland plays a role in the production of this cutaneous picture. Our series of cases is in agreement with that of Curth,[13] that the onset and spread of acanthosis nigricans at the beginning or during the age of puberty would be evidence in favor of the belief that the gonads or sex hormones are also involved in the propagation of the juvenile type of this disease. The association of obesity with juvenile acanthosis nigricans in the recorded cases indicates that one may find mild acanthosis nigricans more frequently in obese adolescents if it is carefully sought for.

SUMMARY AND CONCLUSIONS

A case of acanthosis nigricans juvenilis associated with obesity is reported, with a compilation of cases from the medical literature.

Observations on dysfunction of the endocrine glands associated with benign acanthosis nigricans warrant serious consideration that glandular dysfunction, particularly involving the pituitary, suprarenals and gonads, may play an important role in the cause of benign acanthosis nigricans.

The obesity associated with juvenile acanthosis nigricans is usually pituitary in type. The age of onset and spread of juvenile acanthosis nigricans at the beginning or during the age of puberty are evidence in favor of the belief that the gonads or sex hormones play a role in the propagation of the juvenile type of the disease. These findings tend to strengthen our views concerning the importance of endocrine dysfunction involving the pituitary gland and gonads in the benign juvenile type of this disease associated with obesity.

It is our belief that the tinea versicolor and dermatophytosis infections found in our patient were coincidental and had no etiologic relationship to the underlying patches of acanthosis nigricans.

The association of obesity with benign juvenile acanthosis nigricans indicates that a careful search for mild forms of this disease in obese adolescents, particularly those suffering from glandular dysfunction, may reveal cases in which acanthosis nigricans has not been diagnosed.

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MADURA FOOT (MYCETOMA)

First Report from the Isthmus of Panama

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SOME TIME ago it was interesting to note the lack of bibliographic data on actinomycosis on the Isthmus of Panama, whereas there were various reports from Puerto Rico,[1] Cuba [2] the southern part of the United States [3] and Mexico,[4] which, like the isthmus, bound the Caribbean Sea. Also the geographic location of the isthmus, with its warm, humid climate, would appear to make it a favorable region for any type of mycotic infection. The later diagnosis in the first 2 cases of chromoblastomycosis,[5] when I commenced my investigations, and in the third and fourth cases (as yet unreported), observed in the last fifteen months, leads me to believe that actinomycosis can be encoun-

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From the medical staff of the Hospital Santo Tomas.

1. Carrión, A. L.: Estudio micologico de un caso de micetoma por Cephalosporium in Puerto Rico, Mycopathologia **2**:165, 1940. Carrión, A. L., and Knott, J.: Mycetoma by Monosporium Apiospermum in St. Croix, Virgin Islands, Puerto Rico J. Pub. Health & Trop. Med. **20**:84 (Sept.) 1944. Stokes, R. J.: Un caso de pie de madura, Bol. Asoc. méd. de Puerto Rico **34**:138 (April) 1942. Busó Carrasquillo, R.: Madura Foot in Puerto Rico, ibid. **30**:452 (Dec.) 1938.

2. Trespalacios, F., and de Laosa Capote, O.: Sobre un caso de micetoma del pie, Vida nueva **54**:445 (Dec.) 1944.

3. (*a*) Allison, H.: A Case of Mycetoma, Texas State M. J. **8**:168, 1912. (*b*) Sutton, R. L.: Mycetoma in America, J. A. M. A. **60**:1339 (May 3) 1913. (*c*) Pagenstecher, G. A.: Madura Foot, More Properly Called Mycetoma, ibid. **78**:1363 (May 6) 1922; (*d*) Third Case of Mycetoma, ibid. **82**:1692 (May 24) 1924. (*e*) Gammel, J. A.; Miskjian, H., and Thatcher, H. S.: Madura Foot (Mycetoma), Arch. Dermat. & Syph. **13**:66 (Jan.) 1926. (*f*) Thompson, H. L., and Ikeda, K.: Maduromycosis: Fourth Case Reported in the United States, Arch. Surg. **16**:764 (March) 1928. (*g*) Brindley, P., and Howell, W. H.: Madura Foot in the United States, South. M. J. **25**:1022 (Oct.) 1932. (*h*) Burns, E. L.; Moss, E. S., and Brueck, J. W.: Mycetoma Pedis in the United States and Canada, with a Report of Three Cases Originating in Louisiana, Am. J. Clin. Path. **15**:35 (Feb.) 1945. (*i*) Peters, J. T.: A Clinical Cure of Madura Foot, Am. J. Trop. Med. **25**:363 (July) 1945.

4. Cicero, R. E.: Micetoma, Gac. méd. de México **7**:291, 1912. Ocaranza, F.: Micetoma en Sonora, Bol. de cien méd. México **4**:433, 1913-1914. González Ochoa, A.: Micetoma por Actinomices Mexicanus Boyd y Crutchfield, 1921, en Mexico, Rev. d. Inst. salub. y enferm. trop. **3**:303 (Dec.) 1942.

5. Calero, C.: Chromoblastomycosis: Report of Two New Cases Observed in the Isthmus of Panama, Arch. Dermat. & Syph. **54**:265 (Sept.) 1946.

tered on the isthmus in any of its clinical forms, in particular, Madura foot (mycetoma), or that it has been recognized but has not been reported in the past.

My study has confirmed my previously indicated suspicions, showing 1 case of actinomycetoma and 1 of thoracic actinomycosis; furthermore, it has shown that in Hospital Santo Tomas since the year 1922 there have been 2 other patients with the diagnosis of Madura foot (although without laboratory examinations) and that in Gorgas Hospital, in the Canal Zone, this same diagnosis has been made in a patient, with pathologic reports and cultures of the strain as confirmation. In several other records (4 cases) there is a suggestion of this disease; however, there is no laboratory confirmation, nor do the clinical descriptions in these records correspond to the classic picture of Madura foot.

The clinical history of the case of Madura foot I have studied is as follows:

REPORT OF A CASE

M. A., a 42 year old white man, who still lives in the town of his birthplace, Las Lomas (province of Chiriqui, Republic of Panama), is a farmer and works wearing *cutarra* (sandals). He entered Hospital Santo Tomas with elephantiasis and multiple fistulas with granular, lobulated edges of the left foot, of four years' duration. The history revealed that the disease had commenced shortly after the patient had received a hard blow on the left ankle, which produced ecchymoses, edema and intense pain, requiring four days' rest in bed. The first change that the patient observed was the formation of a small purulent, painless mass over the left metatarsal arch, cyanotic in color, from which dark blood drained on opening of the mass; a crust formed over the mass, and on its removal there was always an abundant serous discharge with a disagreeable odor and occasionally bloody. Eight days later a second pustule developed near the primary lesion, which progressed in the same manner; a third, fourth and even fifth lesion developed, the new one always appearing at the time of formation of the crust of the preceding lesion nearby and with the same physical and subjective characteristics as the primary one. Since then, with periods of regression and exacerbation other lesions have occurred with a slow, chronic progression, without any tendency to spontaneous healing and, on the contrary, accompanied with edema of the foot, gradually causing a loss of its normal lines of concavities; the foot has finally become so painful and deformed that walking has been impossible (fig. 1).

His medical history in other respects was noncontributory, with the exception that he had had malaria and an appendectomy for chronic appendicitis.

Physical examination (inspection) revealed an anemic, emaciated person with atrophy of the left thigh and leg as far as the inferior third portion, where there were three scars from previous fistulization, which had healed well. There was a decided increase in the diameter of the left foot where the natural concave appearance had been lost. The toes were moderately edematous (increasing from the big toe to the small toe) and without separation and were at a distinct level from the sole. The surface of the foot was irregular because of multiple, wide-based nodules (none pedunculated), some confluent (easily distinguished by their size), from the majority of which drained a seropurulosanguinous liquid, of a disagreeable odor, with a variable number of yellowish white granules. There were many other nodules, without drainage, that were covered by a thin layer of skin, through which

one could see crystal clear fluid, confirmed by aspiration. The vertex of the nodules corresponded to the site of drainage; each nodular fissure led to the formation of a fistula, which became evident by a central depression and which temporarily might become covered with a crust, the removal of which immediately started new drainage. However, some lesions had healed completely, decreasing in size but becoming harder. I noted that the patient held his foot in semiflexion, and it appeared to be shorter than the right foot; also, the left foot was in valgus position, with the tip of the foot in abduction (the internal maleolus was nearly in an anterior position).

Examination by organs gave essentially normal results in each aspect, with the exception of moderate hypertrophy of the lymph nodes in the left triangle of Scarpa and of the atrophy, previously mentioned, in the lower left extremity, with the following measurements: 15⅝, 13⅜, 12, 10⅖ and 8⅗ inches (40, 34, 30, 26 and 21 cm.) in the right extremity, in comparison to 13½, 11½, 9, 8½ and 8 inches (34, 29, 22, 21 and 20 cm.) respectively in the left extremity, at the levels of middle and inferior thirds of the thigh and at the superior, middle and inferior thirds of the lower leg. The circumference of the diseased foot at its middle portion was 13½ inches (34 cm.), in comparison to 8½ inches (21 cm.) in the normal foot.

Laboratory Examination.—The urine was normal in all respects. The feces presented eggs of Uncinaria; the Kahn reaction was negative. Examination of the blood chemistry for glucose, nonprotein nitrogen, albumin nitrogen and globulin nitrogen, icteric index, van den Bergh reaction and albumin-globulin ratio showed values all within normal limits. There was moderate anemia, of a normocytic hyperchromic type; the platelet count was normal; the sedimentation rate was 37 mm. in an hour. A moderate leukocytosis (73 per cent polymorphonuclears) with lymphocytopenia was present. Roentgenograms of the left foot showed that the density of the soft tissues was too great to permit the study in detail of the osseous (fig. 2) structures, but one could see necrosis of the calcaneum and general osteoporosis of the bones of the foot, which had advanced as far as the inferior aspect of the tibia and fibula. A roentgenogram of the thorax revealed no pulmonary or cardiovascular changes.

Histopathology.—The microscopic examination of the excised nodule showed decided acanthosis, with projection of the rete pegs into the underlying tissues. The dermis showed dense fibrous tissue and leukocytic infiltration (especially of the polymorphonuclear type) greater in the papillae about the blood vessels, which showed thickened walls, due to proliferation of their adventitial coats. The subcutaneous tissues showed dense fibrous and hyalinized connective tissue infiltrated with polymorphonuclear leukocytes and macrophage cells; foci of polymorphonuclear cells, unassociated with the presence of fungous organisms, surrounded by fibrous tissue and macrophages; vessels with thick walls surrounded by polymorphonuclear infiltration; small capillaries with diminished lumens due to thickening of its wall; vessels partially occluded (fig. 3*A*) by pink or blue stained-filamentous forms, surrounded by polymorphonuclear leukocytes and macrophages, and ray fungus (fig. 3*B*) stained brown in its central part and pink in the outer zone without definite filamentous forms being visible close to the pink outer zone, as has been described by some investigators; however, "clubs" forms were distinguishable. The ray fungus was always surrounded by a thick layer of polymorphonuclear infiltration; at its periphery were seen granulation tissue heavily infiltrated with polymorphonuclear leukocytes and macrophages and, more peripherally, fibrous tissue infiltrated with plasma cells. In the slides studied no giant cells were encountered.

Mycologic Examination.—Examination of the granules between slide and cover glass showed the characteristic actinomycotic forms of ray fungus (fig. 4) with the club-shaped forms at the periphery and filaments in the central part. The granules were whitish yellow.

Culture of the granules, after being washed in isotonic solution of sodium chloride and cut into small portions, was made on Sabouraud's medium at room

Fig. 1.—Appearance of the foot at the time of the patient's admission to the hospital, with nodular formations, sinus tracts and moderate elevation of the toes (above the plantar surface).

Fig. 2.—The density of the soft tissues is too great to permit the study in detail of the osseous structures. Nevertheless one can see necrosis of the calcaneum and general osteoporosis of the bones of the foot and inferior aspect of the tibia and fibula.

temperature (28 C. [82.4 F.]) and at incubator temperature of 37 C. (98.6 F.). One mycotic colony growing among contaminant staphylococcus colonies was clearly visible after nineteen days' incubation; the surface was wrinkled, of a creamy consistency and whitish yellow, becoming more yellowish with time. Transplantation

of the colony, to obtain a pure culture, showed a definite growth (fig. 5) within thirty-six hours of a strain, whitish, moist and always with a wrinkled center, sometimes depressed and other times decidedly elevated. The colony was surrounded generally by a smooth zone with radial striations; frequently outside this zone was

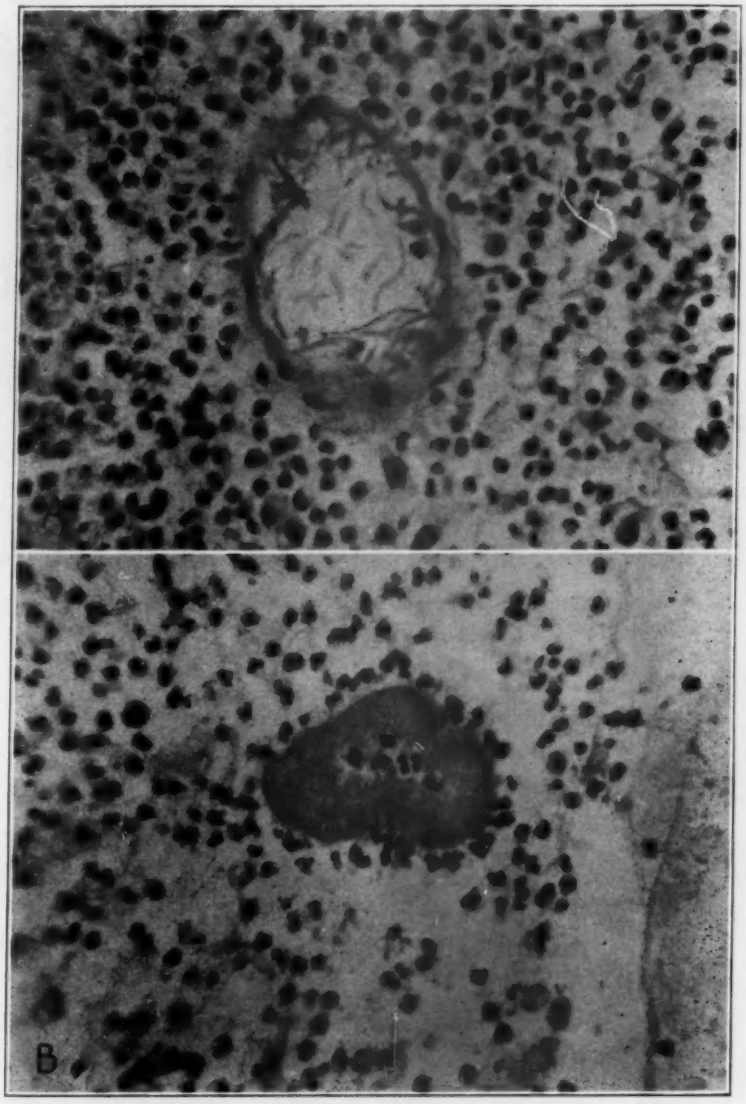

Fig. 3.—*A*, vessel partially occluded by filamentous forms, surrounded by polymorphonuclear leukocytes and macrophages. × 460. *B*, ray fungus with its central and outer portions without definite filamentous forms being visible but with characteristic "club" forms at the periphery, surrounded by polymorphonuclear leukocytes and macrophages. × 460.

seen a third smooth zone, whose edges were slightly elevated. The culture always became more yellow with age; its odor was similar to that of damp earth.

Microscopic examination of the strain growing on the slides showed abundant filament forms, with a nearly imperceptible cellular membrane, nonsegmented, occasionally with refringent granules, branching, without formation of chlamydospores (fig. 6) and of variable length. Besides the long filaments one could observe shorter forms, some bacilliform (occasionally with one end wider than the other,

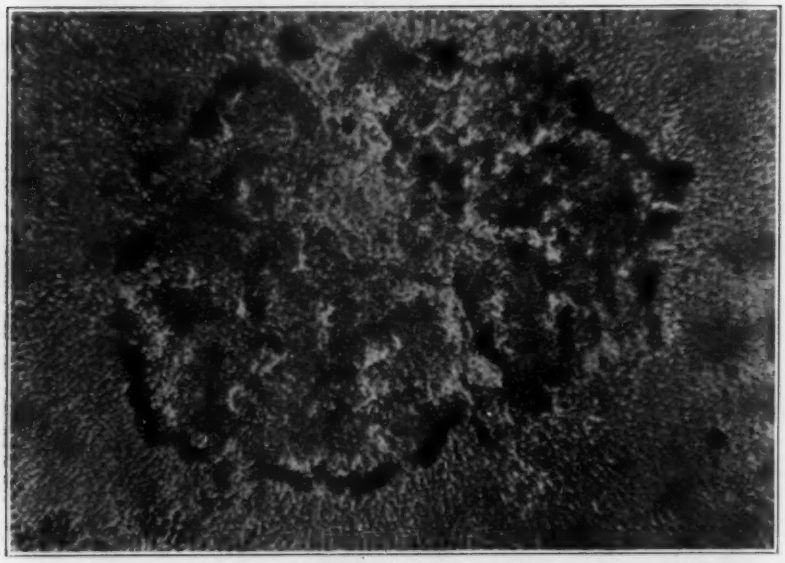

Fig. 4.—Characteristic actinomycotic forms of the ray fungus, with the "club" forms at the periphery (from the granules). × 120.

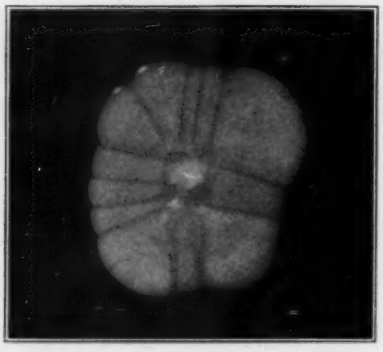

Fig. 5.—Pure culture at the fourth week of incubation at room temperature (28 C. [82.4 F.]).

especially in the old tubes) and even coccic forms. Also, a few large round forms, of 3 to 4 microns in diameter, were seen (fig. 6). Staining of a thin smear of the fungus in suspension of isotonic solution of sodium chloride revealed that the developed organism was not acid fast and that it was gram-positive.

Fermentation tests were employed, with these results (the reading was made at forty-eight hours): There was a fine pellicle with granular growth on the surface

of all the mediums used (glucose, saccharose, maltose, mannitol and lactose); no gas formation was present in any of the carbohydrate mediums used; in the bottom of the tubes there was a fine precipitate of granular growth, and, finally, the liquid itself was clear in appearance in all the mediums.

With the same purpose I cultured in blood agar at incubator temperature of 37 C.; a definite growth was observed within twenty-four hours of a strain with the same microscopic appearance previously reported; the last reading of the culture, after seven days, did not show any hemolysis.

The culture of the fungus growing in gelatin at 37 C. and kept afterward in a refrigerator did not show any liquefaction. In the incubator at 37 C. again, there was liquefaction, and this process continued consistently.

Inoculation of Animals.—Although it will be the subject of another paper, I wish to report now that 4 white rats were inoculated intraperitoneally and 1 rabbit

Fig. 6.—Microscopic appearance of the culture in isotonic solution of sodium chloride. Abundant filamentous forms, some bacilliform (occasionally with one end wider than the other) and others coccoid. × 960.

intravenously with pure culture of the micro-organism in suspension of isotonic solution of sodium chloride and that repeated inoculations in the same animals were made in the same way five times at ten day intervals. I did not observe any positive result in these experimental animals.

Four white rats were inoculated subcutaneously with granules taken directly from the lesion on the foot and pulverized and suspended in isotonic solution of sodium chloride; in all these animals a nodule appeared at the site of the injection; the nodules increased slowly in diameter till the twelfth day; in only 1 of these animals the nodule diminished in size and disappeared; in another 2 the nodules opened through the skin and discharged a pasty mass, following which the lesion healed in a week. The microscopic examination of the pasty mass did not reveal any filament, and its culture was sterile. In the last one the nodule removed at the end of the second week was taken for microscopic examination.

Two rabbits and 4 white rats were inoculated subcutaneously with pure culture in suspension of isotonic solution of sodium chloride; a nodule appeared at the site of the injection, which increased slowly in diameter until the sixth day and remained without any change in the rabbits until the eighth week, when I removed them for microscopic examination, as I shall report in another paper. In the rats the nodules diminished in size and disappeared in the third week, with only one exception; in this animal I removed the nodule at the end of the third week for microscopic examination.

Treatment.—The etiologic diagnosis of the disease having been established, with the determination of the mycologic species, treatment was initiated with sulfadiazine[6] in doses of 1 Gm. every four hours (day and night). After the third week, with the blood sulfadiazine level between 6 and 13 mg. per hundred cubic centimeters of blood, there was a definite improvement in the patient, with decrease in the size of the foot, in the amount of fluid drainage from the fistulous tracts and in the number of granules, which, having been obtained easily previously, were now obtained with difficulty. After seven and a half weeks, however, it was necessary to stop the medication (212 Gm. of sulfadiazine were given) because of anorexia, insomnia, nausea and vomiting and because of an itchy and scaly erythematous dermatosis in plaques located on the face and anterior aspect of the thorax. The patient's resistance required a change of therapy, and after seven days' rest from medication I commenced with administration of sodium propionate,[7] obtained from the E. I. Du Pont de Nemours and Company in this city, and prescribed the dosage of 1 Gm. every four hours (day and night), increasing it to 2 Gm. after four days. After three days, however, it was again necessary to cease medication, not only because of nausea, asthenia, insomnia and anorexia but also because of the increased volume of the leg and secretion from the fistulous tracts, opening again.

I was unable to convince the patient that he should rest a few days and repeat the sulfonamide treatment in shorter series. He asked to be discharged from the hospital at this time.

COMMENT

In conjunction with the records of this hospital and Gorgas Hospital, in the Canal Zone, a review shows that since 1922 in 2 cases Madura foot has been diagnosed, with laboratory confirmation. The ages of the patients were 42 and 43 years respectively. Both were farmers, acquired the infection on the Isthmus of Panama, gave a history of having been traumatized previously in the same foot in which the dis-

6. González Ochoa, A., and Zozaya, J.: Influencia de la sulfanilamida "in vitro" sobre el desarrollo y estructura de Microsporum canis, Sporotrichum schenckii y Actinomyces asteroides, Rev. d. Inst. salub. y enferm. trop. **3**:145 (June) 1942. Keeney, E. L.; Ajello, L., and Lankford, E.: Studies on Common Pathogenic Fungi and on Actinomyces Bovis: II. In Vitro Effect of Sulfonamides, Bull. Johns Hopkins Hosp. **75**:393 (Dec.) 1944. Peters.[31]

7. González Ochoa, A., and Ruiloba, J.: Acción del propianato de sodio "in vitro" sobre Actinomyces mexicanus y Cephalosporium sp.; ensayo terapéutico en micetomas producidos por estos hongos, Rev. d. Inst. salub. y enferm. trop. **5**:83 (June) 1944. Keney, E. L.; Ajello, L., and Lankford, E.: Studies on Common Pathogenic Fungi and on Actinomyces Bovis: I. In Vitro Effect of Fatty-Acids, Bull. Johns Hopkins Hosp. **75**:377 (Dec.) 1944.

ease developed afterward and had the lesions localized in the lower left extremity. One was born in Barbados and the other one in the Republic of Panama (province of Chiriquí). One was a Negro, and the other one was a white person.

The macroscopic appearance of the feet in the 2 cases was the classic picture of Madura foot, with its sinus tracts draining almost constantly malformation of the foot, with impossibility of walking or standing on the foot, odor and similar characteristics, such as were described in India by Gill (1842) and by Vandyke Carter (1860); furthermore, it showed that there was no clinical difference between the forms encountered here and the cases reported in Mexico,[4] Puerto Rico,[1] Cuba [2] and the southern part of the United States.[3]

Study of the fungus in the first patient, for whom the diagnosis was confirmed (according to the pathologic report by Dr. W. C. Cox, of the Gorgas Board of Health, who examined the foot and inferior third of the leg after amputation), revealed aerobic, thick and filamentous forms, generally septated and branching, which produced chlamydospores in culture. Examination of the purulent material from the fistulas never revealed filaments, but spores were observed, which aided in the etiologic diagnosis. Neither in the pus nor in the histopathologic preparations were any characteristic actinomycotic granules or ray fungus observed. From the previous data the diagnosis of Madura foot was made, and the type of fungus present was determined as being of the family Streptomycetaceae.

Study of the fungus of the second patient revealed an aerobic strain with fine filamentous formation, branching and a hyalin-like membrane which was nearly imperceptible, unsegmented and broke readily, forming small masses of bacilli and cocci (a few large spores, of 3 to 4 microns in diameter, were encountered) gram-positive and not acid fast; chlamydospores were not formed. Cultures of the fungus developed an odor resembling that of damp earth. In the purulent exudate, as well as in the biopsy preparation, were observed characteristic granules and ray fungus. Also, in the tissue examined at biopsy there were filaments (which stained red in some slides and blue in others), without "club" formation,[8] but surrounded by a fibrous ring and abundant leukocytic infiltration (especially polymorphonuclear) outside the periphery.

A study of these strains necessary to establish the difference between the two strains leads to the conclusion that the first type, according to the modern concepts of Waksman and Henrici,[9] belonged to the

8. Kessel, J. F., and Golden, E. B.: A Comparison of Strains of Actinomyces Recovered from Human Lesions, Am. J. Trop. Med. **18**:689 (Nov.) 1938.

9. Waksman, S. A., and Henrici, A. T.: The nomenclature and Classification of the Actinomycetes, J. Bact. **46**:337 (Oct.) 1943.

family Streptomycetaceae Waksman and Henrici (without establishment of its genus or species); the second type corresponded to the family Actinomycetaceae Buchanan, genus Nocardia Trevisan, species Nocardia asteroides (Eppinger) Blanchard.[10]

The classification of Chalmers and Archibald,[11] classic and useful regardless of the newer ones, is still retained, however, with the belief that the distinct types of pathogenic fungi recognized as etiologic agents of Kaempfer's disease (1712) or Madura foot of Colebrook (1846) or mycetoma of Vandyke Carter (1860) [12] by their microscopic appearance may be placed in one of the two groups called actinomycosis and maduromycosis. In accordance with this concept, each of our 2 cases corresponds to one of the mentioned groups: the case of Dr. Cox corresponds to maduromycosis (mycetoma) and my case to actinomycosis.

Inoculations were made successively in rabbits and white rats from pure culture in suspension of isotonic solution of sodium chloride and from granules pulverized in suspension of isotonic solution of sodium chloride (intravenously in the rabbits; intraperitoneally in the white rats) without producing the disease. The subcutaneous inoculation of pulverized granules in isotonic solution of sodium chloride in white rats gave rise to nodules, some of which opened spontaneously; another one diminished in size and disappeared; in the only one removed for microscopic examination it was impossible to isolate the same inoculated organism. The subcutaneous inoculation of pure culture in suspension of isotonic solution of sodium chloride in 2 rabbits and 4 white rats gave rise to formation of nodules in each animal; at the end of the eighth week I removed the nodules in the rabbits; in the white rats the nodules diminished in size and disappeared in the third week with only one exception; the nodule of this animal was removed at the end of the third week for microscopic examination, as I shall report in another paper.

The insistence of the patient to be treated medically showed that sulfadiazine,[6] regardless of the age of the disease and the stage of advancement of the lesions, gave the best results; this leaves the impression that if the treatment can be initiated early in the disease the possibilities of cure should be better and the prognosis under these conditions should not be so hopeless as it was in the past. Suspension of treatment because of resistance and sensitization was necessary, and further treatment was refused by the patient. The use of sodium pro-

10. Binford, C. H., and Lane, J. D.: Actinomyces Due to Nocardia Asteroides, Am. J. Clin. Path. **15**:17 (Jan.) 1945.

11. Chalmers, A. J., and Archibald, R. G.: A Sudanese Maduromycosis, Ann. Trop. Med. **10**:169 (Sept.) 1916.

12. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, ed. 3, New York, William Wood & Company, 1919, pp. 967 and 2110.

pionate [7] had to be stopped almost immediately because of the patient's being unable to tolerate it, with an exacerbation of local symptoms resulting.

SUMMARY

The existence of Madura foot (mycetoma) on the Isthmus of Panama is reported for the first time.

It is certain that the condition in the first case corresponded to the known type called maduromycosis (mycetoma) (Streptomycetaceae Waksman and Henrici) and the second to the type actinomycosis (Actinomycetaceae Buchanan). I am unable to indicate the genus or species of the first one because the data at hand are incomplete. The fungus recovered in the second case corresponded to the genus Nocardia Trevisan and to the species Nocardia asteroides (Eppinger) Blanchard.

The treatment was of a medical nature in spite of the advanced state of the lesion. I feel sure that in early and localized lesions the use of sulfonamide drugs (I used sulfadiazine) not only will prevent the progress of the same but also will cure the infection, because in my case there was definite improvement. I also noted that the use of sodium propionate not only produced an intolerance but also aggravated the local symptoms, necessitating the immediate withdrawal of this medicament.

Dr. J. M. Nuñez, Chief of the Medical Department of Hospital Santo Tomas, and Dr. H. C. Clark, director of the Gorgas Memorial, gave me suggestions and laboratory privileges. Dr. M. Warner cooperated in translating this report.

PEMPHIGUS VULGARIS

A Study of the Blood Picture

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CLINICAL and laboratory studies have led me to believe that pemphigus vulgaris is a generalized infection.[1] Evidence to support this belief was sought by an examination of the blood picture and is presented in this paper.

Generalized infections produce qualitative and quantitative alterations in the blood picture, which include (*a*) leukocytosis, which is generally due to an increase in the number of cells of the polymorphonuclear series; (*b*) changes in the polymorphonuclear leukocytes (these include an increase in the proportion of immature and a corresponding decrease in that of the mature cells; the severer the degree of infection or toxemia resulting from infection, the higher is the proportion of immature cells; in this paper the term "immature" is used to designate the polymorphonuclear leukocytes in which the nucleus is indented but not segmented and also Schilling's staff forms with unsegmented nuclei, which may be in the shape of a T, U or V; all segmented polymorphonuclear leukocytes whose nuclei contain two or more lobes have been regarded as mature cells; illustrations of immature cells are given in figures 7 and 8 of plate III and of mature cells in figures 9, 10 and 11 of the same plate of Wintrobe's "Clinical Hematology"[2]; additional diagrammatic information on these cells is also to be found in figure 28 of that work[3]); (*c*) decrease in number of eosinophils, with increasing severity of infec-

From the New York Hospital and the Department of Medicine, Cornell University Medical College, and the Long Island College Hospital and the Department of Dermatology and Syphilology, Long Island College of Medicine.

1. (*a*) Grace, A. W.: Pemphigus: Effect of Pemphigus Serum on the Leukocytic Picture of Rabbits, Arch. Dermat. & Syph. **29**:885 (June) 1934; (*b*) Pemphigus: Evidence in Support of a Bacteremia as an Explanation of Certain Terminal Changes in the Blood Picture, ibid. **30**:22 (July) 1934. (*c*) Grace, A. W., and Suskind, F. H.: An Agent, Transmissible to Mice, Obtained During a Study of Pemphigus Vulgaris, Proc. Soc. Exper. Biol. & Med. **37**:324, 1937. (*d*) Grace, A. W.: Pemphigus, M. Clin. North America **22**:1345, 1938. (*e*) Grace, A. W., and Suskind, F. H.: An Investigation of the Etiology of Pemphigus Vulgaris, J. Invest. Dermat. **2**:1, 1939.

2. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942, p. 98.

3. Wintrobe,[2] p. 123.

tion and vice versa; (*d*) reduction in number of lymphocytes,[4] and (*e*) simple chronic anemia, occasioned by defective formation of blood rather than by excessive loss or destruction of blood. In such an anemia there is generally a parallel decrease in the number of corpuscles, the quantity of hemoglobin and the volume of packed cells without change in either the size or the hemoglobin content of the cells.

The normal figures for the blood picture are, as given by Wintrobe[5]:

Red blood cells	Men:	5,400,000 ± 800,000 per cubic millimeter
	Women:	4,800,000 ± 600,000 per cubic millimeter
Hemoglobin	Men:	16.0 ± 2.0 Gm. per hundred cubic centimeters
	Women:	14.0 ± 2.0 Gm. per hundred cubic centimeters
White blood cells		5,000 to 10,000 per cubic millimeter

The normal differential white cell count in adults[6] is as follows: myelocytes 0 per cent, unsegmented polymorphonuclear leukocytes 3 to 5 per cent, segmented polymorphonuclear leukocytes 54 to 62 per cent, lymphocytes 25 to 33 per cent, monocytes 3 to 7 per cent, eosinophils 1 to 3 per cent and basophils 0 to 0.75 per cent.

MATERIALS AND METHODS

The studies reported in this paper were carried out on 11 persons, 10 of whom died from pemphigus vulgaris in the New York Hospital after continuous periods of hospitalization, which ranged from twelve to one hundred and seventy-six days. The eleventh person was studied only from the aspect of pruritus and eosinophilia in pemphigus vulgaris. He was under continuous observation for sixty-one days at the Long Island College Hospital, from which he was discharged, to die within six months at Kings County Hospital. The oldest was 68 and the youngest 24 years of age. The average age was 47 years, and there were equal numbers of men and women. Nine persons were Jewish, 1 was a Gentile and the other a Negro. The duration of the disease among the group varied from three months to four years. The progress of all, with the exception of 2, was steadily downhill after admission. In the case of the 2 exceptional persons, who were hospitalized for one hundred and seventy-six and one hundred and four days respectively, definite clinical improvement occurred, and it continued for many weeks. It was manifested by a reduction in the temperature and in the number of lesions and an increased sense of well-being; the degree of betterment, however, was insufficient to warrant discharge from hospital. Complete remission had occurred in 4 persons prior to admission to the hospital and had lasted in 1 case for as long as six months.

It is clear that the persons whose examinations are reported here were in the terminal stages of the disease. It was for that reason that they were chosen, for it was felt that, at that point of the illness, there would be fewer factors influencing the action of the etiologic agent on the blood picture. Such factors as remained, however, were considered from this aspect and included clinical remission and relapse, impending death, increase of body temperature and administration of sulfanilamide.

4. Piney, A.: Recent Advances in Haematology, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1931, p. 143.

5. Wintrobe,[2] p. 72.

6. Wintrobe,[2] p. 125.

The examination of the blood was either performed or supervised by the technician of the Hematological Department of the New York Hospital; in the case of the eleventh person the work was carried out at the Long Island College Hospital.

TOTAL WHITE CELL COUNT

Determinations of the total white cell count were made at one to six day intervals in 9 persons, 6 of whom were also studied from the point of view of red cell count and hemoglobin content. One hundred and seventy-eight counts were made, with an average of 17,410 leukocytes per cubic millimeter; the lowest average reading in any person was 10,910 and the highest 35,600. Consideration of the count in the patients showed that a maximum figure of 48,000 was reached in 1; of between 30,000 and 40,000 in 4; of between 20,000 and 30,000 in 2, and of between 10,000 and 20,000 in 2. Minimum counts ranged from 5,350 to 14,300. The highest point was generally attained during the last weeks or days of life. Thus, it occurred in 5 persons in the last five days and in 2 others in the third week before death. In 1 person, although the maximum figure was found over three months before the end, the count during the last month of life was consistently higher than that of any similar interval of his one hundred and seventy-five day period of continuous observation. In the case of the ninth person the final determination was made too long before death to be considered in this connection. Unlike the results in the case of the red cell count, there were only 2 instances in which the final white cell count was the lowest to be reached; in 3 of the remaining 5 it was above the average for the particular person.

The effect of change in the clinical condition on the total white cell count was studied in the same 2 persons and at the same time as were employed for a similar investigation of the red cell count and hemoglobin content. In view of the fact that the highest white cell count is generally to be found in the final weeks of life, the figures for the period of the relapse which terminated in death were not included in this study, on the grounds not only that they would increase unfairly the count during deterioration but also that they could not be compared with the findings in a subsequent remission. In both persons there was a definite increase in the total white cell count as the clinical condition became worse; in 1 instance the figure rose from an average of 19,630 in improvement to 25,550 in deterioration and in the other from 16,750 to 23,670.

In 10 persons a relation was sought between the body temperature and the white cell count by taking the rectal temperature at the time that blood was withdrawn for the count. One hundred and seventy-eight temperature readings were made, with a maximum, mean and minimum of 104 F., 100.3 F. and 97.4 F. respectively. The mean tem-

perature may appear low for a group of persons in the final stage of a disease which is due to a virus whose effects are generally lethal for human beings. Temperature above 103 F. is, however, unusual in pemphigus vulgaris; less than 4 per cent of the thermometer readings in our series were above that figure, and none was encountered higher than 104 F. The average white cell count was calculated for each of eight levels of temperature, which began at 97 F. and increased by 1 F. at each level to a maximum of 104 F. With the exception of the levels 98.0 F. to 98.9 F. and 104.0 F. to 104.9 F. the deviation of the white cell count, at any level, from the average for all patients at all temperatures (17,410 cells) was less than 1,000 cells. In the two exceptional instances the count exceeded the average by approximately 3,000 and 4,000 cells respectively.

The effect of sulfanilamide on the white cell count was studied in 1 person, in a temporary state of remission, who received 42.3 Gm. of the drug in nine days. The concentration of total sulfanilamide at the end of that period was in the blood serum 13.33 mg. and in the blister fluid 11.76 mg. per hundred cubic centimeters. The fluctuation in the white cell count during the administration of the drug was too great to enable a definite trend to be detected in the number of cells, but the average daily count for the first half of the treatment period—23,280 leukocytes—was 23 per cent higher than that for the second half. This difference may have been due either to the depressant action of the sulfanilamide on production of leukocytes or to its bacteriostatic effect on the cutaneous organisms which begin to invade the blisters of pemphigus in numbers sufficient to be detected on culture about eighteen hours after the appearance of these lesions. In the case under observation, the high concentration of the drug in the blister fluid enabled the latter to remain bacteriologically sterile in the unbroken bullae for at least forty-eight hours.

POLYMORPHONUCLEAR LEUKOCYTES (NEUTROPHILS)

Observations on the relative proportion of polymorphonuclear leukocytes in the differential white cell count were made at one to six day intervals in 8 persons. One hundred and seventy-one counts were made with average percentages of total, mature and immature neutrophils of 66.9, 30.9 and 36.0 respectively. The lowest and highest average readings in any person were for the total 47.6 and 75.6, for the mature 7.2 and 40.9 and for the immature 24.7 and 55.1 per cent respectively. The lowest and highest single readings were for the total 31.3 and 86.5, for the mature 0.0 and 70.4 and for the immature 6.2 and 82.1 per cent respectively.

The effect of remission and relapse on the relative distribution of mature and immature cells was observed in 2 persons. In the case of the first, during a period of remission of forty-two days, the average propor-

tion of mature polymorphonuclear leukocytes accounted for 48.1 and of immature cells for 18.7 per cent of the total number of leukocytes; in one hundred and twenty-eight days of relapse the proportions of these cells were 37.5 and 27.2 per cent respectively. Corresponding figures for the second person were as follows: In a remission of thirty days mature and immature cells comprised 43.8 and 31.3 per cent, and in a relapse of twelve days they comprised 15.6 and 58.1 per cent respectively.

The effect of impending death on the polymorphonuclear leukocytes was studied in 3 persons whose clinical progress was steadily downhill from the day of admission to the hospital until death and whose duration of hospitalization was sufficiently long to enable a satisfactory comparison to be made of the blood cell count in the first and second halves of the period in the hospital. As the end of the second half was occasioned by the death of the patient it is obvious that the clinical condition in this half of the illness was worse than in the first. In the case of 1 person hospitalized for forty days, the proportions of mature and immature cells were 37.3 and 30.7 per cent respectively during the former half and 11.6 and 45.1 per cent during the latter. Corresponding figures for the second person were as follows: In the former half of a period of hospitalization of thirty-four days mature and immature cells comprised 13.5 and 47.9 per cent, and in the latter half they comprised 1.4 and 61.8 per cent respectively. For the third person, hospitalized for twenty days, the figures for the mature and immature cells were for the former half 31.3 and 44.7 per cent and for the latter 21.2 and 60.0 per cent respectively. The influence of impending death on the proportions of mature and immature polymorphonuclear leukocytes was also noted in 2 other persons, whose periods of observation before death were fourteen and twelve days respectively. The percentage of mature cells fell in the first person from 40.4 to 28.3 and in the second from 38.0 to 26.9. The proportion of immature cells correspondingly rose in the first person from 24.3 to 39.2 and in the second from 29.6 to 40.4 per cent. Death followed the last observation in each person at intervals of ten and five days respectively. Counts were also made in 4 persons within two days of death and on the last day itself. In these the proportion of mature cells ranged from 0 to 16 and of immature from 41 to 69 per cent, and the combined totals of mature and immature polymorphonuclear cells were 81, 62, 69 and 54 per cent respectively.

In order to determine the extent to which the proportion of polymorphonuclear leukocytes was influenced by the presence of bacterial microorganisms in the bullous fluid, 1 person, in a temporary state of remission, received 42.3 Gm. of sulfanilamide in nine days. The concentration of total sulfanilamide at the end of that period was in the blood serum 13.33 mg. and in the blister fluid 11.76 mg. per hundred cubic centi-

meters. Daily differential white cell counts during the period of treatment and the subsequent nine days revealed the average proportion of mature cells to be 32.7 and 52.3 and of immature forms to be 45.0 and 22.0 per cent for those periods respectively.

EOSINOPHILS

Consideration of eosinophilia in pemphigus vulgaris was made in 8 persons, 7 of whom were observed for periods ranging from one hundred and four to twelve days before death. The eighth person was included in this study solely in virtue of the severe pruritus of the scalp which accompanied a generalized eruption of pemphigus. After the first twenty-three days of hospitalization the pruritus disappeared, but the patient was retained in the hospital for a further period of observation of thirty-eight days. During the stage of pruritus there was an average eosinophilia of 16.7 per cent, with a maximum and minimum of 24.0 and 12.0 per cent respectively. On the disappearance of itching the proportion of eosinophils immediately fell to below 6 per cent and remained there until the patient's discharge from hospital. No other observations were made on this patient.

The maximum degree of eosinophilia occurred at intervals ranging from sixteen to thirty-six days before death and was in 6 nonpruritic persons 4, 6, 9, 9, 11 and 20 per cent. In none of these was there an eosinophilia of more than 6 per cent during the last thirteen days of life, nor did any nonpruritic person attain a level of more than 6 per cent after having once reached a figure of zero.

The effect of clinical remission on eosinophilia was studied in the 2 patients already referred to in this connection. In 1, who was nonpruritic, the eosinophils constituted 4.1 per cent in remission and 2.4 per cent in relapse. The other received, as a therapeutic measure, sixteen subcutaneous and three intravenous injections of an emulsion of mouse brain containing the inactivated RP virus.[7] The first injection was given one hundred and seventy-two and the last eight days before death. Severe attacks of itching coincided with relapse, and death occurred after a series of acute asthmatic attacks. The average percentage of eosinophils was 1.8 during the forty-two days of the first remission, 12.8 during the forty days of the first relapse, 6.5 in the forty-eight days of the second remission and 14.0 during the thirty-six days of the second relapse, which terminated in death.

The influence of impending death on the proportion of eosinophils was observed in 2 persons, who were hospitalized for forty and thirty-five days respectively. For the first the average figure for the first half of the period of hospitalization was 6.0 per cent and for the second,

7. Grace, A. W.: The Etiologic Agent of Pemphigus Vulgaris, Bull. New York Acad. Med. **22**:480 (Sept.) 1946.

which terminated in death, 2.3 per cent; in the latter patient the corresponding figures were 10.5 and 2.8 per cent respectively. It was possible to obtain a count on the day of death in 4 persons. Two showed an eosinophilia of 1 per cent, and in the others these cells were absent.

MONOCYTES

Studies were made on 6 persons, in all of whom the proportion of these cells fluctuated considerably and, at times, attained heights much in excess of normal values. The average percentage of monocytes in the persons examined was 4.1, 4.2, 7.0, 10.3, 12.9 and 14.7 respectively and the maximum readings 10, 11, 12, 18, 23 and 32 respectively. The effect of impending death on the proportion of these cells was studied in 2 persons. In 1 the percentage of monocytes in the first half of the period of hospitalization was 10.2 and in the second half, which terminated in death, was 15.4. The corresponding figures for the other person were 13.5 and 7.0 per cent respectively. Clinical remission and relapse were without effect on the proportion of those cells in the 2 persons studied from this aspect. Sulfanilamide therapy did not produce any significant change in the proportion of the circulating monocytes.

LYMPHOCYTES

The proportion of lymphocytes was studied in 9 persons and ranged from 11.4 to 27.4 per cent, the average being 20.1 per cent. There was little difference between the relative distribution of these cells in remission and relapse in 2 persons examined from this aspect. In 1 the figures were 24.8 and 20.4 and in the other 18.2 and 20.4 per cent respectively. In 2 other persons the influence of approaching death on the proportion of lymphocytes was studied. In the first the percentage of these cells in the former half of the period was 18.2 and in the latter 24.8 per cent; the corresponding figures for the second person were 17.4 and 17.2 per cent respectively. Sulfanilamide therapy was without influence on the proportion of circulating lymphocytes.

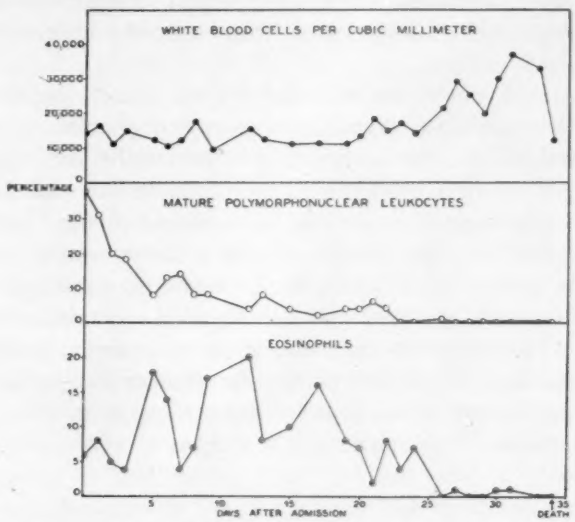
BASOPHILS

Basophils were rarely encountered in any person. The average proportion of these cells in one hundred and seventy-seven counts in 10 persons was 0.3 per cent, with a minimum of 0 and a maximum of 3 per cent.

RED CELL COUNT AND HEMOGLOBIN CONTENT

Determinations of the red cell count and hemoglobin content were made at intervals ranging from one to eight days in 8 persons. The average of eighty-eight determinations was 3,850,000 for the red cell count and 11.2 Gm. for the hemoglobin content. In 5 persons the highest

figures were found on admission and varied from 3,430,000 to 6,610,000 and 9.6 to 14.9 Gm. respectively. Two patients, 1 of whom was hospitalized for one hundred and seventy-six and the other for one hundred and four days, afforded an opportunity to study the effect of clinical improvement on the red cell count and hemoglobin content. In both persons the betterment of the condition was manifested by a reduction in the temperature and in the number of lesions and an increased sense of well-being. The readings in the 2 patients were practically identical and were uninfluenced by the change in the clinical picture. Thus, in 1 case, the cell count and hemoglobin content were 3,850,000 and 11.0 Gm. respectively during improvement and 3,890,000 and 11.5 Gm. in deteri-



Leukocytes, mature neutrophils and eosinophils in peripheral blood of a person in terminal stage of pemphigus vulgaris.

oration. The influence of impending death on the determinations was sought in 5 persons in whom the last examinations were made at intervals of two, three, four, ten and twenty-four days respectively before the end. In all, the red cell count and hemoglobin content progressively declined, over an average period of sixteen days, to levels lower than any previously reached in the same person, the final figures ranging from 2,830,000 and 8.8 Gm. to 4,200,000 and 11.3 Gm.

COMMENT

In the terminal stages of pemphigus vulgaris many of the elements of the blood picture are affected. The most striking departure from normal occurs in the total white cell count and in the relative proportion of mature and immature polymorphonuclear leukocytes. There is a well

marked and constant leukocytosis, whose maximum is attained during the last days or weeks of life. The degree of leukocytosis is more readily influenced by changes in the general condition of the patient than is the cutaneous picture, and its fluctuation can be employed as an index of the trend of the disease. As, however, the leukocytosis is occasioned both by the etiologic agent of pemphigus and, to a less extent, by the presence of bacterial micro-organisms in the bullous and open lesions of the skin, it can be employed for this purpose only when the patient is under treatment with a bacteriostatic agent. The body temperature is, as a rule, elevated only to a moderate degree, and changes in the clinical condition are not reflected in changes in the temperature chart; death may occur with or without fever. The degree of leukocytosis is independent of the level of body temperature over the range of 97 F. to 104 F.

The most sensitive index of change in the general condition of the patient is the proportion of immature polymorphonuclear leukocytes in the peripheral blood. As the presence of bacterial micro-organisms in the cutaneous lesions contributes to their number, the immature polymorphonuclear leukocyte count can be employed for this purpose only when the patient is under treatment with a bacteriostatic agent. With improvement in the clinical condition there is a decrease in the percentage of the immature cells and with deterioration an increase, which may reach such a height that no mature cells can be found at death. As the relative proportion of polymorphonuclear leukocytes—the sum of the immature and mature cells—is within normal range in pemphigus vulgaris, an increase in the immature is accompanied with a decrease in the mature cells.

According to Wintrobe,[8] the highest and most constant eosinophilia (10 to 60 per cent) has been observed in pemphigus and dermatitis herpetiformis. It is likely that the cause of the eosinophilia is not the same in these two diseases. Dermatitis herpetiformis has few systemic manifestations, is seldom debilitating and rarely, if ever, fatal and presents a cutaneous picture characterized chiefly by the development of clusters of small vesicles. The intense pruritus associated with the vesicles leads to their decapitation by scratching soon after their appearance. The reparative powers of the skin in dermatitis herpetiformis, however, are such that healing of individual lesions soon occurs. In this disease, then, the eosinophilia is probably associated with the pruritus and consequent scratching, which introduce the patient's own plasma proteins into his skin. In this connection, I have recently observed an attack of typical urticaria following the second intramuscular injection of human immune globulin in a person convalescing from pemphigus vulgaris, who had received the first injection one week

8. Wintrobe,[2] p. 132.

earlier. In contradistinction to dermatitis herpetiformis, pemphigus vulgaris is a systemic disease of high mortality in which the skin presents large and small blisters, crusted and vegetating lesions. Pruritus is infrequent and moderate in degree. Owing to the weak powers of recuperation of the skin in this disease, individual cutaneous lesions persist for long periods, becoming grossly contaminated and malodorous. The presence of such lesions affords an adequate explanation for the occurrence of eosinophilia in pemphigus vulgaris, as it is known that these cells increase in number during the decomposition of body protein.[9] As such decomposition in pemphigus probably begins in the bullae, it would be reasonable to expect to find a massing of eosinophils in association with these lesions. This has actually been found to occur. The bullous fluid when bacteriologically sterile contains a number of leukocytes, of which the eosinophil is frequently the preponderant cell, constituting at times over 80 per cent of the white cells and occurring in a considerably higher proportion than in the circulating blood.[10]

The proportion of eosinophils diminishes with deterioration of the general condition, and when a nonpruritic patient becomes sufficiently debilitated the eosinophil count may fall to zero, after which it does not rise again above normal limits. In the last two weeks of life the eosinophils do not exceed 6 per cent and are usually less; on the day of death they are few or absent.

The terminal stages of pemphigus are associated with a relative and, at times, considerable monocytosis. This increase is probably a reflection of the role of the monocyte as a scavenger of particulate materials and bacteria.[11] Proof exists [1b] that bacteria enter the circulation from the cutaneous lesions. It is, therefore, likely that particulate matter of microscopic size will also find its way into the blood stream through the base of granulation tissue of the lesions.

No relation exists between the degree of increase of monocytes and clinical remission or relapse, the presence of impending death or the administration of sulfanilamide. Monocytosis is, therefore, an even less sensitive index of the general condition in pemphigus vulgaris than is eosinophilia.

The relative proportion of lymphocytes is diminished to a moderate degree and is unaffected by changes in the clinical picture; there is also no observable effect on the basophil leukocytes.

The red cell count is diminished in pemphigus vulgaris, with a corresponding reduction in the hemoglobin content. Improvement in the general condition, within the limits described in the paper, is without

9. Wintrobe,[2] p. 116.

10. Grace, A. W.: The Significance of Eosinophilia in Blister Fluid and Peripheral Blood in Pemphigus Vulgaris, to be published.

11. Wintrobe,[2] p. 117.

effect on the count and the hemoglobin content. During the last two weeks of life there is a progressive decline in both of these factors to levels lower than any previously reached in the same patient.

In conclusion, the blood picture in pemphigus vulgaris is practically identical with that of a generalized infection. Leukocytosis in this disease, however, does not arise from an increase in the cells of the polymorphonuclear series; it is produced by an increase in the total number of each type of leukocyte present normally in the circulating blood. The absence of neutrophilia may be accounted for on the grounds that the virus of pemphigus,[7] in common with most viruses, is not a pyogenic agent.

SUMMARY

Detailed and repeated studies of the blood picture were made for 11 persons over periods ranging from twelve to one hundred and seventy-six days before death from pemphigus vulgaris. The effect of the following conditions on the picture was noted: clinical remission and relapse, impending death and increase of body temperature and administration of sulfanilamide. The blood picture is practically identical with that of a generalized infection.

An explanation is offered for the occurrence of eosinophilia and monocytosis in pemphigus vulgaris and of eosinophilia in dermatitis herpetiformis.

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NERVE LESIONS OF LEPROSY

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THIS paper deals with the pathologic and bacteriologic aspects of leprosy as it affects the peripheral nerves.

In a paper read by us [1] before the Section on Dermatology and Syphilology at the Ninety-Third Annual Session of the American Medical Association, June 10, 1942, we presented the arguments in favor of the pathologic classification of the forms of leprosy introduced by the South American dermatologists. This insists on the presence of nerve lesions in almost every case of leprosy, regardless of the clinical type, and on the importance of distinguishing the lepromatous from the tuberculoid type of this disease, especially from the public health and epidemiologic points of view. At that time we had studied the pathologic changes of the cutaneous lesions in a large number of cases of leprosy and found them in general accord with the South American classification into lepromatous, tuberculoid and nonspecific types. We also remarked then that the pathologic changes were identical whether the lesions affected the skin, the nerves or the viscera. The pathologic study of the nerve lesions of leprosy has been undertaken since then, and we have now additional proof that the structure of the lesions of the nerves coincides with that of the lesions of the skin.

The lepromatous patients with profuse tuberous cutaneous manifestations usually show clinical involvement of the nerves of the large trunks such as the ulnar, median and saphenous nerves and others in a moderate degree. However, the most remarkable clinical neuritis is found in the tuberculoid type of leprosy, often in conjunction with cutaneous lesions but at times in the form of almost exclusive neural

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Hot Springs, Va., June 10, 1946.

From the Department of Dermatology and Syphilology of the University of Habana Medical School and the Hospital "Calixto Garcia," V. Pardo-Castello, M.D., director.

1. Pardo-Castello, V., and Tiant, F. R.: Leprosy: The Correlation of Its Clinical, Pathologic, Immunologic and Bacteriologic Aspects, J. A. M. A. **121:** 1264 (April 17) 1943.

manifestations, showing enlarged terminal nerves, enormously thickened nerve trunks and areas of cutaneous anesthesia without change in the color or the structure of the skin, although often causing muscular atrophies. These are the cases which were classified under the caption of "neural leprosy" by the International Congress of Leprosy held in Cairo, Egypt,[2] and which, we propose to demonstrate, should be considered as tuberculoid leprosy with predominant location in the peripheral nerves.

We chose for our studies the ulnar nerves of lepromatous patients and the ulnar as well as the superficial branches of the median nerves of patients with the so-called neural types of leprosy. Some of the latter also had cutaneous lesions of the maculopapuloid and annular leprids as well as muscular atrophies, reabsorption of the terminal phalanges and mal perforans plantaris.

Fig. 1.—Chronic neuritis of the ulnar and antibrachial nerves in a case of tuberculoid leprosy (so-called neural leprosy).

THE LEPROMATOUS NERVE LESIONS

Sections made of the ulnar nerves in cases of this type of leprosy with profuse cutaneous lesions showed a structure similar to that of the cutaneous manifestations; the nerves were affected throughout, including the perineural tissues, and the infiltrating cells were those of the histiocytic vacuolar type with apparently empty spaces, similar to those observed in the cells of Virchow. The nerve fibers were degenerated and in many places destroyed, being surrounded by the aforementioned cellular infiltration. Lymphocytes accumulated in the periphery of the groups of vacuolar cells. No fibrosis or scarring was apparent in the sections observed by us. The cellular infiltration in some nerve filaments was in the form of patches of vacuolar cells, while the rest of the nerve tissue seemed little affected.

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2. Resolutions and Reports of the International Congress of Leprosy Held in Cairo, J. Egyptian M. A. **21**:138 (March) 1938.

Sections of lepromatous nerves stained with *Nachtblau* according to the Hallberg-Reenstierna method[3] showed enormous numbers of Hansen bacilli stained in bright blue, in bundles, starlike clumps, pairs and singly, among the nerve fibers, in the perineural tissue and in the vacuolar spaces of the cellular infiltrate. The impression was that the tissue did not react greatly to the large number of germs present.

Fig. 2.—Chronic neuritis of the femoral cutaneous nerve in a case of tuberculoid leprosy (so-called neural leprosy).

THE TUBERCULOID NERVE LESIONS

Sections were made of the superficial nerves in cases in which only nerve thickening existed, without cutaneous manifestations, and also of the ulnar nerve in cases with cutaneous tuberculoid lesions. In the two types the pathologic changes were exactly alike, showing that the cases of so-called pure neural leprosy are in reality cases of tuberculoid

3. Hallberg, V.: A New Method of Staining Tubercle Bacilli (with a Note by J. Reenstierna on the Use of This Method for Staining Leprosy Bacilli), Acta med. Scandinav. **108**:12, 1941.

leprosy affecting the peripheral nerves, with or without coincident cutaneous lesions.

The sections showed a miliary arrangement, resembling under small microscopic power the lesions of tuberculosis as found in lupus vulgaris and in some sarcoids. This type was composed of thick infiltrations of lymphocytes and epithelioid cells surrounding large multinucleated cells of the giant type. Staining with the Hallberg-Reenstierna method and with Ziehl-Neelsen stain showed no bacilli. In no case of this type could we find necrosis or caseation; the lesions were the exact counterpart of those found in tuberculoid leprosy located in the cutaneous structures.

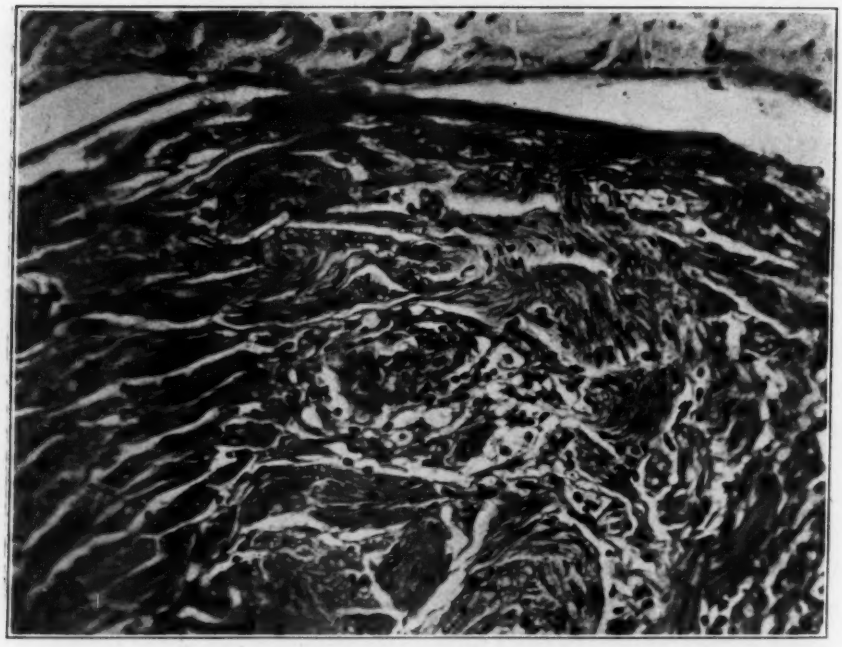

Fig. 3.—Lepromatous infiltration in a branch of the ulnar nerve in a case of lepromatous leprosy. Notice the large vacuolated cells.

In 2 cases with exclusive involvement of the nerves we found the formation of the so-called nerve abscess, in reality the mass caseation of the tuberculoid manifestations, with complete destruction of the neural tissues. This necrotic material was collected in the center of the nerve and appeared surrounded by a ringlike accumulation of histiocytes, epithelioid cells and lymphocytes with occasional giant cells. In 1 case the necrotic material opened a path to the outside and collected under the skin, resembling an abscess, which perforated the skin and emptied itself on the surface. This is the type reported by Rabello, of

Rio de Janeiro,[4] under the name of "colliquative neuritis." In this type we found a few bacilli and some acid-fast granules in the tissue surrounding the necrotic center but none in the necrotic material itself. Nerve scarring and fibrosis were the natural termination of these two types of tuberculoid neuritis.

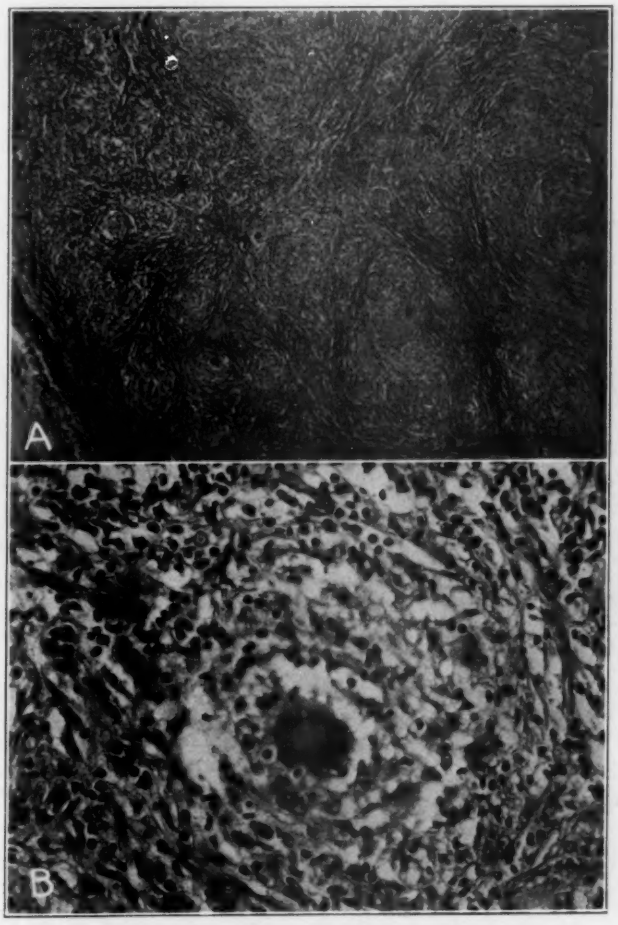

Fig. 4.—*A*, typical miliary infiltration of tuberculoid leprosy affecting a branch of the antebrachial nerve. Specimen from the patient shown in figure 1. *B*, giant cell and vacuolated histiocytes surrounded by lymphocytes in tuberculoid leprosy of the nerves. Enlargement of the section shown in *A*.

SUMMARY AND CONCLUSIONS

1. All patients with leprosy present involvement of the nerves to a greater or lesser degree.

4. Rabello, E., Jr.: Etiologie générale et pathogénie de la lèpre tuberculoïde, Rev. brasil. de leprol. **6**:291 (Sept.) 1938.

2. The pathologic study of nerves in cases of the lepromatous type showed the typical structure as observed in the cutaneous manifestations, with accumulations of vacuolar cells and enormous numbers of Hansen bacilli scattered throughout the nerve fibers. There was little tendency to react on the part of the nerve tissue.

3. The pathologic study of enlarged nerves from patients with cutaneous lesions of the tuberculoid type showed structures that could be identified as the counterpart of those found in the skin, consisting of miliary tuberculoid or sarcoid changes and centered with multinucleated giant cells. These lesions end in fibrosis and destruction of the nerves.

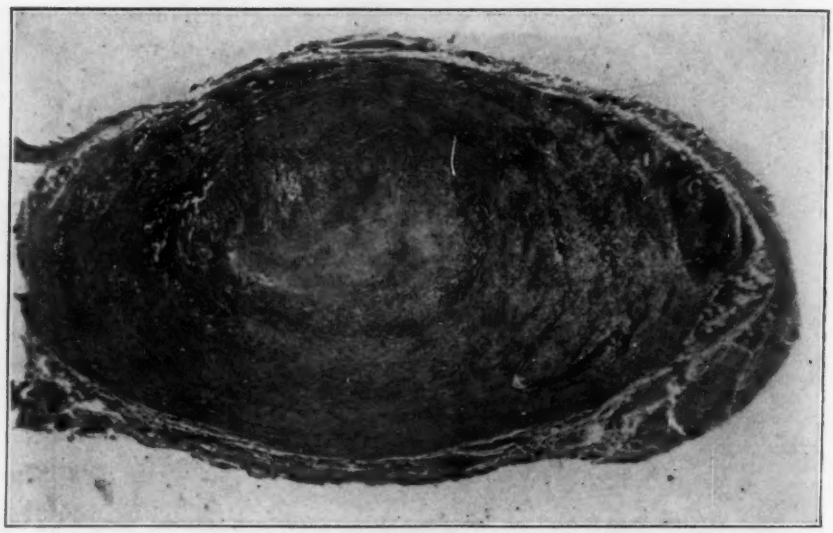

Fig. 5.—Cross section of a nerve affected with the colliquative type of tuberculoid leprosy, showing central necrosis.

4. The pathologic study of nerves from the patients with thickening of the peripheral nerves, with or without cutaneous lesions, which are considered by those who accept the Cairo classification of the types of leprosy as typical of "neural leprosy," showed also a tuberculoid structure and terminal fibrosis. In some rare cases the process goes on to necrosis, with the formation of caseation collected in the center of the affected nerve or else of a pseudoabscess, which empties itself by adhering to the skin and perforating the cutaneous structures (colliquative neuritis of Rabello). No acid-fast bacilli were demonstrable in these cases except in the inflamed tissues surrounding the necrotic areas in 1 of our cases; these were found in small numbers and mostly as acid-fast granules.

5. The Hallberg-Reenstierna method of staining Hansen bacilli with *Nachtblau* stain was found easy and distinctive, the bacilli showing bright blue.

6. In our opinion these studies show that the so-called neural leprosy belongs to the tuberculoid type and corresponds immunologically and bacteriologically to this type as described first by Jadassohn and later by the South American dermatologists. We believe that there is no reason to maintain the existence of "neural" and "cutaneous" forms of leprosy, but these designations may be used to express the location of the lesions, but only with a topographic meaning.

ABSTRACT OF DISCUSSION

DR. BRAULIO SÁENZ, Habana, Cuba: I wish to congratulate Dr. Pardo-Castello on his excellent paper, which is useful for the diagnosis in certain cases of leprosy which may be difficult to recognize, even for those who are acquainted with the various types of this condition. Also, I wish to express my appreciation for the privilege of opening the discussion on this valuable contribution dealing with the nerve lesions observed in leprosy.

The picture corresponding to lepromatous leprosy is well known, both clinically and histopathologically, the difficulties arising in cases of so-called neural and tuberculoid leprosy. In these the features are not so well defined, and many points should be carefully considered before one arrives at a definite conclusion. For instance, the responsible etiologic agent of the various granulomatous infections is only rarely demonstrated in the sections; on the other hand, sometimes it may have disappeared, and in other cases it may be produced by the action of the toxins. Then it must be admitted that some other criteria are needed for establishment of a correct diagnosis. The study of the infiltrate in itself does not help either, because it is difficult at times to differentiate the tuberculoid structure of various conditions, such as lupus vulgaris, some sarcoids and mycosis, conditions in which the infiltrate is extremely similar.

It is for this reason that this paper is useful, because it emphasizes the changes early observed in the nerves in all types of leprosy, changes that are detectable not only on the lesions of the skin but also in places of the skin which are supposed to be absolutely normal.

Tuberculoid leprosy was first described by Jadassohn in 1898, but it was not well established as an entity until 1927 by Darier. Since then, many contributions have been made; a few have been made in Europe, but most of the work has been done by Wade, in South Africa; Wade and Rodriguez, in the Philippines; Lowe, in India, and Reiss, in China. In Brazil should be mentioned the papers of Motta, Seminario and Gaviña Alvarado, Grieco and Rabello Jr., and in Argentina the work has been done by Baliña y Bassombrio, J. M. Fernandéz, Schujman and Castañé, these last three men under the direction of the late Dr. Enrique Fidanza, who was an honorary member of this association.

At the meeting of this association in 1938, at Del Monte, Calif., I read a paper on tuberculoid leprosy, and at that time I emphasized the necessity of a study of all cases of tuberculoid leprosy from a histologic point of view, mentioning the constant presence of anesthesia or hypesthesia of the lesions, the scarcity or absence of Mycobacterium leprae, the positive Mitsuda reaction and the benign course of the disease. As Dr. Pardo-Castello stated, the lesions of the nonmyelinic fibers

of the nerves of the upper corium are not easy to detect, because of their simple structure, the changes being more pronounced on the deeper myelinic nerves because they are more differentiated and resistant than the superficial ones of the upper corium. For this reason, the biopsy specimens should be taken deep enough in the subcutaneous tissue in order to study the myelinic fibers, where the changes are more pronounced and lasting.

In regard to the opinion of Dr. Pardo-Castello that neural leprosy is a type of tuberculoid leprosy, I do not agree with him, but in my experience I have observed that muscular atrophy in pure neural leprosy is not often seen, as is the rule in the mixed types of the disease. I have followed a score of patients who presented great involvement of the superficial cervical plexus. The nerve branches could be seen protruding under the skin. Nevertheless, these patients did not suffer from the acute neuralgic pains that accompany the neuritis of lepromatous leprosy. The disease, with treatment, regressed and disappeared; the nerve did not show any more enlargement, and, besides, even the anesthesia or hypesthesia regressed and what was left in some cases was a slight numbness.

In addition to the study of the infiltrate in tuberculoid leprosy, so clearly expressed by Dr. Pardo-Castello, I think that it is well to mention the opinion of Dr. Castañé, of Rosario, Argentina. He said that it is worth while to state that the infiltrate in these cases adopts always a peculiar picture or pattern; that is to say that the initial lesions are observed next to the nerve branches, not near the blood vessels. The infiltrate pushes the blood vessels toward the periphery. This special arrangement he calls para-arterial neural infiltration, which he considers typical of tuberculoid leprosy, affirming that it is present in 74 per cent of all cases that he has studied and stating that it is the best differential diagnosis between tuberculoid leprosy and any other disorder producing tuberculoid infiltration.

I have had no experience with the Hallberg-Reenstierna *nachtblau* staining method for detecting Mycobacterium leprae; I have always used Ziehl, Klingmüller and Gallego stains, but I shall be glad to try it in future cases.

Dr. Wiley M. Sams, Miami, Fla.: I have been close to the problem of leprosy in that I live but a short distance from Cuba and have, in thirteen years, had the opportunity to observe 17 cases, a relatively small number in comparison with those reported in neighboring countries.

My interest is in the problem of early diagnosis, and I am entirely in accord with the South American classification which has been presented. I am interested now in the epidemiology and in the infectious nature of some of the problems that arise in my community. Most of the patients that I have had the opportunity to observe present lesions of the tuberculoid type, with only 2 or 3 showing predominantly lepromatous lesions. I have observed in 1 case the transition from the tuberculoid into the lepromatous type when the patient had a coexisting severe illness. Is it possible that such may occur without regard to the condition manifested or to the patient's immunologic reaction. If persons with tuberculoid lesions who react positively to lepromin would maintain this status permanently, it would simplify many of our problems in handling such cases.

Dr. Norman N. Epstein, San Francisco: I should like to ask Dr. Pardo-Castello if he would discuss the value of the cutaneous tests in differentiating types of leprosy.

Dr. Cornelius F. Lehmann, San Antonio, Texas: Mr. Chairman, I am delighted to hear Dr. Pardo-Castello, who has had such an extensive study of this subject, clearly define to us and bring out this point that leprosy is not to be

divided into just neural and lepromatous. We read that the lepra bacillus has an affinity to nerve tissue. For a long time I felt that the first tissue that was ever affected was the nerve. When I see a case in which I want to substantiate a diagnosis, the first thing I look for is enlarged nerves or nodulations, and I have had the experience in numerous instances in these tuberculoid types in which I have failed absolutely to detect at first examination any enlargement of nerves or nodulations. I recall 1 patient who presented recurrent leprosy fever. That was later diagnosed as bullous erythema multiforme on numerous occasions, and it was three or four years before nodules developed from which the bacilli could be recovered.

I have had little experience with the histamine and lepromin tests and should like Dr. Pardo-Castello again to bring out the value of that in the early diagnosis. I have had several instances in which the diagnosis was difficult in early cases because the patients presented only two or three lesions that were of the tuberculoid type.

Dr. Fred D. Weidman, Philadelphia: I first read of the *nachtblau* method in the Norwegian literature in connection with Schaumann's disease, in which Schaumann himself reported the demonstration of tubercle bacilli in the lymph nodes by the Hallberg technic. Inasmuch as I have not had a chance to use it, I should like to know what his advantage might be over the usual Ziehl-Neelsen technic.

All of us know that Dr. Pardo-Castello has a most extensive acquaintance with leprosy and knows the literature thoroughly, and I should like to ask him why it is that, contrary to the case for the tubercle bacillus, this other acid-fast organism so regularly elects nerve tissue. We think of nerve tissue as a tissue that is particularly rich in lipid substances. Is there anything in the literature to indicate that there is a physicochemical explanation, based on a special kind of lipid content perhaps, or other factors in the leprosy bacillus which determine its selection of nerve tissue?

Dr. V. Pardo-Castello, Habana, Cuba: I want to thank you gentlemen for the discussion: The concept of leprosy from the point of view of public health is of the greatest importance, because in the countries where leprosy is endemic, such as in my country and others in South America, it is absolutely impossible, or practically so, to segregate all patients. It would be beyond all possibilities from the economic point of view. It should be about as difficult as to try to segregate all patients with tuberculosis into hospitals or sanatoriums. Therefore, we must find out who are the patients that are really dangerous to the community; those are the patients with lepromatous leprosy. I do not see any reason why the patients with tuberculoid leprosy should be segregated. Those patients must be and should be under sanitary supervision, but there is no reason to raise such a teriffic noise about 1 simple case of tuberculoid leprosy affecting the nerves, particularly the case of so-called neural leprosy, for instance.

The importance of lepromin in the prognosis of leprosy is great. Lepromin is not a diagnostic test. That is, many patients with leprosy are lepromin positive, and others are lepromin negative. Those that are lepromin negative are the patients with lepromatous leprosy; all those with the contagious type of the disease and all those without defensive powers are lepromin negative. On the contrary, all the patients with tuberculoid leprosy, those who have adequate defenses, that is, who show few, if any, bacilli in their tissues and none in the secretions are lepromin positive. Therefore, there is a simple test from the point of view of public health to show which patients should be segregated and those that should not.

The simplest test, of course, is to show the presence of Hansen bacilli in the secretions and the tissues, but it is not easy in all cases to demonstrate the presence of these bacilli. Therefore, the lepromin test would be of prognostic value in that a positive reaction would occur in a patient who is probably poor in bacilli and a patient that has adequate defenses, one that has little possibility of transmitting the disease to another human being.

It is easy to perform the lepromin test. It is done just as an intradermal tuberculin test, and the preparation of the antigen is also easy with a lepromatous piece of tissue. I shall not go into the technic because that would take too much time.

As to the histamine test that one of the discussers mentioned, of course that is a diagnostic test of interrupted conduction of the peripheral nerves and applies to any peripheral neuritis that causes destruction of the nerve fibers. It is a fine test to distinguish and to diagnose leprosy in persons who will not cooperate, such as children and persons who refuse to consider their sensations abnormal—persons who are tested for pain sensation or for heat sensation or thermal sensations in general—and refuse to cooperate. We want to remember that there are persons who want to fool the physicians and that there are children and feebleminded or primitive persons who do not understand what the difference between contact and pain means.

In that case the histamine test will give the answer; that is, the histamine will not show the typical triple response of Lewis but will produce a wheal and no surrounding erythema. That shows that there is peripheral neuritis of the destructive type. That, of course, would be true in vitamin B deficiency; it would be true in destruction of the peripheral nerves due to injury. While that might also be true in alcoholic neuritis or arsenical neuritis, the histamine test is useful in leprosy in differentiating from syringomyelia producing similar sensory manifestations of the peripheral parts of the body. In that case, the peripheral nerves are not really affected; that is, the conductibility of the nerves is preserved. Therefore, the histamine would be of value in distinguishing between these two diseases.

Finally, as to the stain, I am indebted to Dr. Weidman for the Hallberg-Reenstierna stain. I did not know where to get the *Nachtblau,* which is a German dye and is off the market now. I think that a substitute in the form of a similar dye is going to be made in this country. It is easy to employ, and it will show the most abundant blue bacilli, both in tuberculosis and in leprosy. We do not have the difficulty of using too much of our acid alcohol and decoloring all our bacilli, as often happens, particularly in leprosy bacilli, which are not so acid fast as the bacillus of tuberculosis.

I do not know, in answer to Dr. Weidman, and I do not think that we have had explained satisfactorily the reason for the preference of the leprosy bacillus for the peripheral nerves. We know that they go up from the skin, and it has been proved to a certain extent that the lesions begin in the skin and the bacilli are carried there by the circulation; then they attack, by preference, the peripheral nerves, the terminations and the nerve endings in the skin and travel in an ascending, centripetal course, without ever arriving, so far as has been shown, at the spinal cord. They reach as far as the roots of the cord but not the cord itself.

TOPICAL PENICILLIN THERAPY

II. The Principles of Local Therapy with Penicillin Ointment Mixtures

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CINCINNATI

THE PRINCIPLES OF LOCAL THERAPY WITH PENICILLIN OINTMENT MIXTURES

THE EFFECTIVE antimicrobial properties of penicillin make its range of application extensive. Early in the investigative history of this antibiotic its topical action was recognized. Since that time, attempts have been make to employ penicillin in the treatment of numerous diseases of the skin. Because of the many factors involved in the topical application of a relatively unstable chemotherapeutic agent, the use of penicillin in ointment form for cutaneous infections has not been a simple matter. Our own experiences with more than 400 cases, however, show that, when properly prepared and rationally employed, penicillin ointment mixtures are of value in dermatologic therapy.

With penicillin ointments in their present state of development, certain important factors must be considered in their preparation, storing, dispensing and application to insure maximum therapeutic effectiveness.

1. *Preparation.*—Factors to be considered are: (1) stability, (2) dispersion of the penicillin in the proper medium, (3) diffusion from the base, (4) irritation and (5) concentration.

Stability: Stability depends on the absence of water in the ointment, the use of a relatively stable penicillin salt such as calcium penicillin rather than sodium penicillin and the maintenance of comparative sterility during preparation. The temperature of the mixture during preparation should not exceed 15 C. and should be preferably lower. The presumed expiration date should be recorded.

Dispersion: Since it is imperative that the penicillin come into direct contact with the infectious agent in maximum concentration, the anti-

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biotic must be dispersed throughout the vehicle in the form of a fine emulsion. Some factors influencing dispersion are consistency, viscosity and thoroughness of mixing.

Diffusion: Another factor which is responsible for the concentration of penicillin in the tissue fluids is the rate of diffusion of the antibiotic from the base. The base should be so chosen as to allow uniform but not too rapid diffusion into the tissue fluids.

Irritation: Most of the simple bases used in water-free ointments, such as petrolatum, liquid petrolatum, peanut oil, beeswax, synthetic higher alcohols such as Lanette wax S X and wool fat, are usually not irritating. In a certain, and increasing, percentage (as high as 10 per cent:) of cases penicillin per se may be sensitizing.

Concentration: A concentration of 500 to 1,000 units of calcium penicillin per gram of ointment is preferable in most cases in which use of penicillin ointment is indicated. In our study we have used concentrations as high as 20,000 units per gram and produced no irritation and only rarely increase in sensitization. Comparative studies employing ointments of different concentrations are still in progress.

2. *Storing.*—Calcium penicillin in the water-free bases which are now used requires continued refrigeration before and after dispensing, of 15 C. or lower. Reputable water-free ointments containing calcium penicillin may not lose potency significantly if kept at room temperature for one or two weeks. In some cases, e. g., of impetigo, the application of the ointment is usually maintained for this brief period. Nevertheless, because of variations in the stability of ointments at so-called room temperature and the variation in room temperature conditions, it is advisable to instruct all patients to refrigerate the penicillin ointment prescribed to avoid possible mishaps.

3. *Dispensing and Application.*—A metal ointment tube with a small bore nozzle is the container of preference. There is less opportunity for contamination of the ointment in this container than in a glass jar or metal can. Jars must be sterilized, and ointment should be removed with the aid of a sterile applicator or a knife blade which has been previously sterilized by flaming.

The stability of ointments has been determined by assay of ointments for penicillin activity at repeated intervals, the ointments being stored at room and incubation temperatures as well as various refrigeration temperatures. Preliminary studies have also been made by us to determine the duration of activity of the penicillin after the ointment mixture is applied to the skin. Two methods of penicillin ointment assay have been used.

1. Ether Extraction Method: The penicillin is extracted from the base with ether. The total penicillin extracted from a given weight

of ointment is determined by a serial dilution technic, Bacillus subtilis being employed as the indicator organism.[1]

2. Crude Cup Method: The ointment is placed directly in the penicillin assay cups which have been set into staphylococcic-seeded agar mediums. A comparison of the zone of inhibition with those resulting from the standard ointments and solutions determines approximately the activity of the test ointment.

SIMPLE TOPICAL THERAPY

Simple topical therapy with penicillin ointment mixtures may be distinguished from combined topical and parenteral therapy. The use of penicillin locally depends on the known fact that there are numerous pathogenic micro-organisms which are primary or secondary invaders of the skin and which are sensitive to penicillin. Susceptibility to penicillin is a relative rather than an absolute characteristic. There are organisms which are highly sensitive to extremely low concentrations of penicillin, and there are many more organisms which are less sensitive but which are inhibited by moderate concentrations. In general, the susceptibility of pathogenic micro-organisms in vivo parallels the sensitivity of the organism in vitro. Included in this group of sensitive micro-organisms in relationship to common cutaneous infections are Staphylococcus albus, Staphylococcus aureus, Streptococcus haemolyticus, nonhemolytic streptococci, Diplococcus pneumoniae, Corynebacterium diphtheriae and many others. Theoretically the topical application of penicillin provides a means of placing penicillin in high concentrations in close proximity with the growing sensitive invaders. The amount of penicillin which actually affects the organisms depends on the penetrability of the mixture and the rate of the diffusion of the product from the base. The antibacterial effect of the achieved concentration depends on the duration of contact with the organism. At the present time no adequate method has been worked out to determine the penicillin concentration in the tissue fluid of an infected area of the skin following the application of the antibiotic ointment.

In actual practice considerable knowledge may be obtained through bacteriologic studies of the local lesion and by determining the susceptibility of the isolated organism (s) to penicillin. To determine susceptibility of bacteria, the culture of the isolated organism is tested against penicillin concentrations varing from 1 unit per cubic centimeter to 0.0015 unit per cubic centimeter. The fate of the infectious agent may be followed by repeated cultures during the course of the treatment.

1. Randall, W. A.; Price, C. W., and Welch, H.: Estimation of Penicillin in Body Fluids, Science **101**:365, 1945.

Clinical and laboratory studies with penicillin ointment mixtures demonstrate its comparative usefulness in many types of cutaneous diseases.

Conditions for Which Penicillin is Definitely Indicated.—1. Impetigo: Results with penicillin ointment mixtures are gratifying. The lesions clear rapidly in both acute and chronic cases. Resistant types of impetigo which do not respond to the usual local chemotherapy will often respond quickly to the antibiotic ointment. The ointment is usually applied once daily or more frequently after scrubs with soap and warm water. Perhaps the frequency of application is related to the concentration of penicillin and the persistency of the ointment on the lesion.

2. Superficial Impetiginized Dermatitis: Examples of superficial impetiginized dermatitis are infected contact dermatitis and scabies. The special problem of infectious eczematoid dermatitis is a different cutaneous reaction and is discussed in another section of this report.

3. Superficial Pustular Folliculitis: Results are satisfactory in cases of superficial pustular folliculitis. When facial lesions are treated with the ointment, the patient should be observed carefully because at times in facial areas, in adults especially, penicillin ointments may be sensitizing. The reason for this has yet to be determined.

4. Dermatophytosis with Secondary Pyogenic Infection: Excellent results have been obtained in the treatment of the secondarily infected interdigital type. The course of the primary fungous infection is not influenced.

5. Superficial Wounds: Penicillin ointment may be used to prevent secondary infection.

6. Operative Sites: Penicillin ointments may be used in preference to penicillin solutions in potentially infected or actually infected areas, e. g., when specimens have been removed for biopsies or when circumcisions have been done.

7. Burns: In pressure dressings ointments are used following débridement to prevent infection.

8. Infected Sinus Tracts and Cyst Cavities: Penicillin ointments are useful in infected sinus tracts and cyst cavities.

9. Aphthous Stomatitis: In cases in which penicillin-sensitive streptococci predominate, topical application of the antibiotic is indicated. Comparative studies with troches or lozenges have not been made.

Conditions in Which Penicillin is of Possible Benefit.—1. Infectious Eczematoid Dermatitis: There are several complicating factors to be considered in the treatment of this disease with penicillin ointment. Many of the cases reveal the presence of penicillin-resistant organisms.

Also the patients will often not tolerate greases and the condition will become worse with any type of greasy medicament. When this occurs penicillin solution packs may be used.

2. Pyodermas of the Deeper Type: An example of such a condition is pyoderma gangrenosum. The value of topical therapy is limited to the prevention of contiguity spread of the lesions. Combined parenteral-topical therapy is recommended. When topical therapy is employed and ointments of high concentrations of penicillin are available, 10,000 to 20,000 units per gram may be employed. An experimental study was conducted in which concentrations of 10,000 units per gram and 20,000 units per gram were used in a small group of cases of pyoderma gangrenosum, with some benefit. The investigation in other cases continues.

3. Ulcers: Serious consideration of all etiologic factors must be given in all such cases. If ulceration is on a simple pyogenic basis, lesions may respond to the ointment alone. Mixed infections with the presence of penicillin-resistant organisms make the problem more complex. In the critical evaluation of penicillin therapy, vascular factors, bacteriology, immunobiology and histopathology of the lesion should be studied. Evaluation of nutritional and cardiac status is frequently indicated.

4. Infectious Exanthemas: Penicillin ointment may be used to prevent secondary infection with subsequent scarring, as in varicella.

5. Seborrheic Dermatitis: Satisfactory results have been observed in a few cases, but further investigation is necessary.

6. Sycosis Barbae: Penicillin ointment is unsatisfactory when used alone. When used along with depilation of infected hairs and roentgen therapy and other forms of adjuvant treatment, the reported results are often good.[2]

Penicillin is of no value for (1) deep infections in which the ointment cannot penetrate the infected area (carbunculosis or deep cellulitis); (2) psoriasis; (3) lupus erythematosus; (4) pemphigus; (5) dermatitis herpetiformis; (6) "stasis" eczematoid dermatitis; (7) acne vulgaris (both the papulopustular and the nodulocystic varieties fail to respond), and (8) herpes labialis.

Penicillin is contraindicated (1) in cases in which eczematous penicillin sensitivity is demonstrated; (2) in cases in which the infectious organism is penicillin resistant; (3) when the ointment is nonsterile or inactive (patients should be instructed to notice the expiration date on all commercial penicillin ointments and not accept ointments in which the expiration date has passed), and (4) in cases in which there are contraindications to the use of greases.

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2. Cohen, T. M., and Pfaff, R. O.: Penicillin in Dermatologic Therapy, Arch. Dermat. & Syph. **51**:173 (March) 1945.

COMBINED TOPICAL AND PARENTERAL ADMINISTRATION OF PENICILLIN

Possible indications for combined topical and parenteral use of penicillin are (1) superficial infections with invasion of the blood stream; (2) secondarily infected virus infections, e. g., vaccinia and variola in a case of severe eczema vaccinatum and in a case of Kaposi's varicelliform dermatitis, combined therapy was used to combat widespread staphylococcic infection; in the case of eczema vaccinatum the side of the face to which the ointment was applied cleared much more rapidly than the other, to which no chemotherapeutic agent was applied), and (3) deep pyogenic infections, e. g., pyoderma gangrenosum. There is no evidence that combined therapy produced any more toxic reactions than either parenteral or topical therapy alone. There is also some question as to whether topical use of penicillin is necessary when parenteral therapy is being administered. Studies in the future may reveal that parenteral use of penicillin can do all that topical use of penicillin can accomplish. As indicated previously, theoretically, topical use of penicillin should produce higher local concentrations than parenteral administration of penicillin.

Penicillin assays were made in 2 cases of bulla formation in which parenteral administration of penicillin had been used. The bulla fluid in a case of epidermolysis bullosa showed a relatively lower concentration than the serum which was assayed at the same time. In a case of meningococcemia with gangrene of the extremities, the bulla fluid contained no penicillin. This was not surprising, considering the local circulatory disturbances which were present. Not enough work has been done to be able to compare this study with our work on bulla concentrations during sulfonamide therapy.

OTHER PROBLEMS UNDER INVESTIGATION

Although 500 to 1,000 units of penicillin per gram of ointment is used routinely in the majority of cases, there is no definite information available to prove that this concentration gives maximum results in all cases. We have at present under investigation 68 patients who are being treated with penicillin ointment mixtures with concentrations varying from 5,000 to 20,000 units per gram. This group includes cases of pyoderma gangrenosum, favus, infected sebaceous and pilonidal cysts, ulcers of the legs, impetigo, hidrous adenitis axillaris and infectious eczematoid dermatitis.

Other problems which require further investigation concern penetrability and stability of topical penicillin mixtures. Our attempts to prepare lotions which are as stable as water-free ointments have not been successful. As yet, no studies have been done to determine

whether the type of penicillin, F, X, G or other fractions, is as important in topical as in parenteral therapy.

TOXIC REACTIONS

Preliminary studies indicate that penicillin is a good sensitizing agent. The reactions which are observed are chiefly cutaneous. These may be produced by either parenteral or topical therapy or both. Cutaneous eruptions following penicillin therapy include dermatitis venenata, urticaria, endogenous vesicular dermatitis of the hands, feet, grain and axilla and maculopapular eruptions. In a previous report we have attempted to evaluate 13 cases of eczematous contact dermatitis in which penicillin ointments were employed. In 12 of the 13 cases the reactions were limited to the face. These were characterized by burning, itching and erythema and in the majority of cases reactions occurred within one to three days after the initial application.

Urticaria occurs following parenteral therapy in about 2 to 5 per cent of patients.[3] It is rarely seen following topical treatment. Its appearance may vary in time from one day after the initiation of therapy to one to three weeks following the discontinuation of therapy. Although with parenteral therapy the appearance of urticaria may be no contraindication to continuation of treatment, in cases which manifest infected cutaneous lesions, an associated urticaria is undesirable and application of penicillin should be stopped.

Erythematous vesicular eruptions of the hands, feet, axillas and groin are usually seen in patients under parenteral treatment.

We have seen several unusual cases of reactions to penicillin. One of the patients was a nurse in whom there developed symptoms of serum sickness when she handled penicillin solutions. Dermatitis from penicillin, cutaneous contact, is occurring more frequently in physicians and nurses. The other was a patient in whom there developed angioneurotic edema limited to the face after a nose spray with penicillin solution. We have observed cheilitis from topical applications and stomatitis from topical and, rarely, from parenteral therapy with penicillin.

PENICILLIN MIXTURES

Ointments which incorporate penicillin and other chemotherapeutic agents are being studied. We have employed a mixture of hemin and penicillin for the past year. The rationale for the use of hemin is that this fraction of the hemoglobin complex is reported to stimulate fibroblast proliferation and subsequent epithelization. The conditions treated with hemin-penicillin mixtures included indolent ulcerative lesions

3. Keefer, C. S., and Anderson, D. G.: Penicillin in the Treatment of Infections, New York, Oxford University Press, 1945, p. 938.

which failed to heal under any other type of therapy, sites of excision of tumors of the skin, sites of biopsy and impetigo.

Other chemical bacteriostatic or bactericidal agents which do not affect penicillin in any way may be used to enhance its antimicrobial action in ointment mixtures. The use of chemotherapeutic agents which will inactivate or destroy micro-organisms which are insusceptible to penicillin are especially advantageous.

For the future, mixtures of two antibiotics, as penicillin and streptomycin, would seem to hold great promise. Streptomycin is still relatively unavailable, and its use in ointments will have to await increased production. Penicillin-tyrothricin combinations have also been studied.

PENICILLIN FASTNESS AND TOPICAL THERAPY

The influence of topical penicillin therapy in creating penicillin-fast strains of pathogenic micro-organisms is still to be ascertained. The fact that some lesions will show an early rapid response and subsequently remain unchanged despite continued treatment with penicillin only suggests the possibility of penicillin fastness. Lesions may not respond for other reasons: 1. Penicillin-insensitive organisms may be present. 2. Higher concentrations of the antibiotic may be necessary. 3. The ointment may be inactive. 4. Contributory nonbacteriologic factors may be keeping the lesions active.

CONCLUSIONS

Properly prepared penicillin ointment mixtures of suitable concentration provide a means of therapy for certain selected superficial dermatoses in which the causative organisms are sensitive to penicillin. In order for penicillin ointment therapy to be effective, definite qualifications must be considered. The mixture must be properly prepared, stored, dispensed and applied in the conditions caused by pathogenic micro-organisms which are inhibited by penicillin.

Deep infections, infections of unknown cause, infections in which the organism is resistant to penicillin and contraindications to the use of grease are some of the conditions in which penicillin ointment mixtures should not be used.

Eczematous contact reactions and other forms of reactions of the skin and mucous membrane are seen following topical penicillin therapy. The frequency and severity of these reactions will determine whether topical penicillin therapy in selected dermatoses is to be discarded in favor of equally effective nonsensitizing agents. Moreover, if it is established that topical penicillin therapy also sensitizes a person so that adequate parenteral pencillin therapy cannot be given to that persons in the future, then topical penicillin therapy may have to be discarded.

Brief mention is made of other substances used to enhance the therapeutic efficiency of penicillin in ointment mixtures.

EFFECTS OF GLYCERITE OF HYDROGEN PEROXIDE ON INFECTIONS OF THE SKIN AND MUCOUS MEMBRANES

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ALTHOUGH previous studies have reported on the stability,[1] the antibacterial action,[2] the effects on tissue tolerance [3] and the clinical results achieved with glycerite of hydrogen peroxide in infectious conditions such as otitis media, these have been submitted or have appeared so recently that the composition and properties of the solution require brief description.

An analysis of the field of topical antisepsis demonstrates the fact that hydrogen peroxide possesses virtues which entitle it to a higher position than that which it holds in the opinions of students of this subject. It is true that in the presence of peroxidase its aqueous solutions decompose so rapidly that bacteria are little affected and that in the absence of peroxidase its effects are so mild that it has been given a low phenol coefficient. On the other hand, when its rate of decomposition can be controlled so that the effects of glycerite of hydrogen peroxide can be prolonged, the advantages of an inherently nontoxic, nonirritating and nonallergenic solution are immediately apparent.

Since pure hydrogen peroxide was not available when these studies were initiated, it occurred to Brown, Abramson and Gorin [1] that urea peroxide (a crystalline addition product) could be used to introduce hydrogen peroxide into a nonaqueous solvent both to enhance its stability in the absence of water and to prolong its effects by means of viscoidal solutions such as substantially anhydrous glycerin. It was subsequently discovered that some of the previous attempts in this direction had failed

1. Brown, E. A.; Abramson, H. A.; Gorin, M.; Kauffmann, H. O., and Shanley, E. C.: The Stability of Urea Peroxide in Glycerol J. Am. Pharm. A. (Scient. Ed.) **35**:304-306 (Oct.) 1946.

2. Brown, E. A.; Krabek, W., and Skiffington, R.: A New Antiseptic Solution for Topical Application: Comparative in Vitro Studies, New England J. Med. **234**:468-472 (April 4) 1946.

3. Brown, E. A.: Studies on Tissue Tolerance to a New Glycerol Peroxide Antiseptic Solution, Ann. Allergy **4**:33-39 (Jan.-Feb.) 1946.

because metallic trace elements in the glycerins used had inactivated the peroxides. Oxine (8-hydroxyquinoline), which is itself bacteriostatic because it forms nonionizable salts of the metals necessary for normal bacterial metabolism,[4] acts similarly in solutions of glycerin, prolonging the stability of the peroxide.

The solution now under investigation consists, therefore, of hydrogen peroxide (1.5 per cent) as derived from urea peroxide (4 per cent) dissolved in anhydrous glycerin to which has been added oxine (0.1 per cent). The peptizing and healing properties [5] and antibacterial action [6] of one of the end products, urea, are generally known, as is the bacteriostatic action of oxine.[4] The glycerite of hydrogen peroxide solution demonstrates the antiseptic, deodorant, detergent and hemostatic properties of aqueous solutions of hydrogen peroxide exept that these actions are prolonged. The prolongation of such action is due solely to the surface tension of the glycerin, which confines the liberated oxygen to the solution. As the liberated oxygen leaves the surface of the wound it continuously renews the interface at the infected surface, giving continued antiseptic effects. The glycerin is churned into an oxygen-glycerin cream, which possesses the mechanical characteristics of both the liquid and the ointment type of topical application. The effects of the glycerin, the urea and the oxine are entirely secondary to the action of the hydrogen peroxide.

Tested by a modified agar cup plate method,[2] the solution has been shown to approach closely to tincture of iodine, U. S. P., in its bactericidal and bacteriostatic potency. The studies on tissue tolerance [7] demonstrate a likelihood that at the 95 per cent level irritation might occur in less than 1 per cent of the general population.

The first studies concerned with the treatment of infections dealt with acute and chronic conditions of the ear. In one series [8] of 31 patients, 17 responded with complete remissions in fourteen days and in the remainder the condition cleared by the thirty-eighth day. In the second series [7] the results were consistently duplicated.

The present report describes the effects of the solution as used routinely in 120 patients presenting twenty-three clinical infectious enti-

4. Zentmayer, G. A.: The Inhibition of Metal Catalysis as a Fungistatic Mechanism, Science **100**:294-295 (Sept. 29) 1944.

5. Robinson, W.: The Use of Urea to Stimulate Healing in Chronic Purulent Wounds, Am. J. Surg. **33**:192-197 (Aug.) 1936.

6. Weinstein, L., and McDonald, A.: The Effect of Urea, Urethane and Other Carbamates on Bacterial Growth, Science **101**:44-45 (Jan. 12) 1945.

7. Brown, E. A., and Kelemen, G.: The Use of Glycerite of Hydrogen Peroxide in Inflammatory Aural Conditions, Laryngoscope **56**:556-560 (Sept.) 1946.

8. Brown, E. A., and Owen, W. E.: The Treatment of Chronic Purulent Otitis Media with Glycerite of Hydrogen Peroxide, Arch. Otolaryng. **43**:605-612 (June) 1946.

ties of the skin and mucous membranes. In some patients, two or more dermatologic conditions were present, as, for instance, aphthous stomatitis and paronychia.

In the group of patients studied, the sexes were almost equally represented. The greater majority were adult, the age range extending, however, from 7 to 81 years. In 54 patients, there were clinically recognizable mycotic infections, as dermatomycosis or onychomycosis. In 21 patients the infectious lesions were multiple, with affected toe nails in 11 and finger nails in 9. The clinical types were classified as vesicular (8 cases), squamous (7 cases) and pyodermic (6 cases). Additional sites of infection included the hands in 6 cases, the groin in 4, the perianal region in 3 and the axilla in 1. In 10 patients the ears were affected. Of these, 6 presented infections of the canal and 4 lesions of the junction of the pinna and scalp. In 2 patients there were classic examples of erosio interdigitalis (monilial) and in another 2 tinea barbae.

The organisms present were identified as Trichophyton gypseum, Aspergillus glaucus, monilia, mycelial filaments and yeastlike spores. Bacteria, especialy staphylococci and streptococci, hemolytic and nonhemolytic, were consistently present as primary infection or as secondary invasion.

VESICULAR DERMATOPHYTOSIS

Eight patients presented pruritic, grouped and discrete vesicular lesions confined to the toes but occasionally involving the arch and lateral surface of the heel. A ten minute bath of the feet in aqueous solution of boric acid was prescribed, followed by an application twice daily for twenty minutes of the peroxide solution. All the patients responded with complete remission.

SQUAMOUS DERMATOPHYTOSIS

Seven patients presented scaling, fissuring, pruritic lesions of the toes and the toe webs. Infections of the third or fourth interspaces associated with thickened, sodden, adherent epidermis required two to three weeks of two applications daily, the other scaling lesions clearing in three to five days.

PUSTULAR DERMATOPHYTOSIS

The 6 patients with pustular dermatophytosis presented acute vesiculobullous and pustular lesions characterized by sudden onset, intense pruritus, pain and edema, followed by fissuring, exfoliation and serous oozing and crusting. The bordering red, punctate, papular, discrete and confluent id lesions were present. In all patients there was a subsequent exfoliation and dyshidrosis. All required rest in bed. During the acute stage of the eruption continuous wet dressings with boric

acid, isotonic solution of sodium chloride or solution of aluminum acetate (1 : 30) were used. Glycerite of hydrogen peroxide was applied topically for ten to twenty minutes four times daily and removed with surface sponging with warm water or aqueous solution of zephiran chloride (1 : 1,000). The bullae and vesicles were punctured; exfoliated epidermis was removed and the nails clipped short.

After the acute process had subsided, glycerite of hydrogen peroxide alone was applied twice daily for five to ten minutes and sponged off with warm water. Subsequent treatment included low voltage roentgen rays (80 r unfiltered) at intervals of seven to fourteen days.

Each of the 6 patients in the group returned to his work within two weeks. In 1 patient undergoing his third attack of acute dermatophytosis with a generalized secondary sensitization dermatitis, the glycerite of hydrogen peroxide produced an effect resembling mild dermatitis venenata, and its use was, therefore, discontinued.

TINEA CRURIS

In 8 patients presenting chronic mycotic infections of the groin, perianal and axillary areas, the results were indifferent. In 3 patients, the topical applications were found to be stimulating to the point of irritation. In the others, applications twice daily afforded relief, but not one patient responded with complete recovery.

PARONYCHIA

In 3 patients with paronychia, recovery occurred in three days for 1 and in two weeks for the remaining 2, the solution having been applied as a wet dressing for twenty minutes five times daily.

ONYCHOMYCOSIS

In 5 of the 20 patients presenting onychomycosis, radical removal of the nails was necessary. In 15 the nails were clipped as short as possible. In the first 5 patients, the nail bed was bathed with glycerite of hydrogen peroxide 1 : 15 for ten minutes twice daily and boric acid ointment dressing applied between applications. In all 5 cases, new nails, free of infection, grew normally. The 15 remaining patients soaked their affected nails in aqueous solution of boric acid for thirty minutes daily and applied the glycerite of hydrogen peroxide for ten minutes or longer each day. Although all demonstrated objective improvement, in none was the mycotic involvement completely eradicated. It would appear that in this type of lesion more intimate contact and more prolonged application are necessary to affect the responsible organisms.

TINEA OF THE HANDS

All 3 patients with tinea of the hands presented the typical intracutaneous vesicular and pustular lesions. The intracutaneous vesicles

were denuded, and after soaks in aqueous solution of boric acid, glycerite of hydrogen peroxide was applied topically. In 2 patients there was complete recovery, but in the third, who presented a secondary type of id eruption, the solution appeared to cause irritation, and its use had to be discontinued.

EROSIO INTERDIGITALIS (MONILIAL)

Two patients presented three typical lesions characteristically involving the web of the third and fourth fingers. The lesions were sharply defined, superficially inflamed, chronic and recalcitrant. Yeastlike organisms were demonstrated in scrapings from the borders of the lesions. The treatment consisted in keeping the hands as free as possible from contact irritants, the surface of the lesions being denuded by gentle scrubbing with a soft brush and aqueous solution of boric acid. Moist dressings of glycerite of hydrogen peroxide were applied continuously. All three lesions cleared completely after two to three weeks of treatment.

TINEA OF THE EXTERNAL EAR

In 10 patients of this series there were chronic or recurrent infections of the external ear, of the external auditory canal in 6 and of the junction of the scalp and ear in 4. The lesions were chronic, edematous, inflammatory and painful, with fissuring, exfoliation and cellulitis. The lesions were sponged twice daily with aqueous solution of boric acid or with aqueous solution of zephiran chloride (1:1,000) and dried. The glycerite of hydrogen peroxide was applied for thirty minutes daily. In each case the pruritus was completely controlled, the pain relieved and recovery complete in seven to twenty-eight days.

TINEA BARBAE

In each of the 2 patients with tinea barbae the topical applications of glycerite of hydrogen peroxide proved irritating, and within four days its use had to be discontinued.

LESIONS OF THE MOUTH

The 20 patients with lesions of the mouth presented one or more of the following diseases: aphthae, herpes simplex, gingivitis, lingual tonsillitis, epidermolysis bullosa with oral lesions, traumatic lesions due to a dental plate or to dental extractions, postoperative infections or fissuring of the lips.

In these patients, the glycerite of hydrogen peroxide (1.5 per cent) was diluted 1:15 and prepared immediately before being used routinely as a mouth wash and gargle four times daily, after meals and at bedtime. The clinical effects are listed later.

APHTHOUS STOMATITIS

Of 2 patients, stomatitis had been present in 1 for twelve years and in the other for three years. The lesions were multiple, painful, shallow, inflammatory ulcers varying from 4 mm. to 1.2 cm. in diameter. Both patients were vaccinated with smallpox vaccine, the first twice without success. In the second an intense local reaction and a successful "take" developed.

The diluted glycerite of hydrogen peroxide was used three times daily and at bedtime, the lesions clearing completely, although no previous remission had lasted for more than a few days. The results in the treatment of this disease were so striking as to raise the question as to whether or not the virus causing the lesions might be constantly present in the mouth, its destruction by oxidation removing the local cause. This problem requires further investigation.

HERPES SIMPLEX

Five patients presenting typical localized grouped vesicular lesions on, near or immediately within the margin of the lip responded with complete healing in four to six days following topical application of glycerite of hydrogen peroxide several times daily.

GINGIVITIS

The 4 patients with chronic bleeding, spongy gums, in all of whom Vincent's organisms could be demonstrated, responded readily to applications of glycerite of hydrogen peroxide used twice daily as a mouth wash. A separate report regarding the use of the solution in infections of the mouth is now in preparation.

LINGUAL TONSILLITIS

Two patients presenting painful lingual tonsillitis with injection of the tonsillar pillars and inflammation of the posterior pharyngeal wall used glycerite of hydrogen peroxide, dilute solution, as a gargle five times daily, with complete relief within one day.

TRAUMATIC ORAL LESIONS

In 2 patients who had had badly fitted lower dental plates there were irregular, deep, linear infected and painful ulcerations in the left side of the floor of the mouth. A thin, milky, leukoplakia-like discoloration involved the immediately surrounding mucosa. The ulcers had been persistently present for several weeks despite the fact that the plates had not been used during that time. The dilute solution of glycerite of hydrogen peroxide used as a mouth wash after meals brought complete recovery within twelve days.

In 1 patient who had twelve teeth extracted ten days before presenting himself for treatment, the gums were still loose and spongy and not

healing. There was an obvious fetor. The dilute solution of glycerite of hydrogen peroxide used as a mouth wash thrice daily produced a firm healing of the gums, so that within two weeks the patient could be properly fitted for a dental plate.

In 2 patients presenting postoperative infected lesions, the first a leukoplakia and the second a mucous retention cyst of the lower lip, the dilute solution was given as a mouth wash, both patients responding with complete remission.

FISSURE OF THE LIP

In a single instance a chronic, deep vertical, painful fissure running from the midportion of the mucosa of the lower lip healed in ten days following topical application of the undiluted solution of glycerite of hydrogen peroxide applied five times daily.

EPIDERMOLYSIS BULLOSA

The 1 patient with epidermolysis bullosa, a woman aged 28, had suffered since August 1943 with a continuous, painful, oral, vesicular and bullous ulcerative eruption of the tongue, lips, buccal mucosa, throat and palate, all or any of which were involved at one time or another. The patient was presented at the Boston meeting of the Atlantic Dermatological Society (Feb. 9, 1946). The dilute solution of glycerite of hydrogen peroxide has proved itself to be the most efficacious preparation she has so far used, partially controlling the ulceration and completely relieving the pain. The disappearance of the lesions has not been complete, but the relief attained merits continued irrigations.

IMPETIGO CONTAGIOSA

In 3 patients with impetigo, an aqueous solution of boric acid was used to keep the crusts removed from the facial lesions and the glycerite of hydrogen peroxide solution applied several times daily. Complete recovery occurred in three to five days.

WOUNDS, LACERATIONS AND LOCAL INFECTIONS

In more than 50 patients in whom glycerite of hydrogen peroxide was used postoperatively to sterilize the operative site after completion of a surgical procedure, not one failed to heal by first intention. No infection of any type was noted.

When the solution was used to prevent infection, a single application for two or three minutes was sufficient. When used to irrigate and sterilize local abscesses and the incised lesions of furunculosis, a ten minute application or irrigation twice daily prevented infection. After each application, the material was sponged from the surface of the surrounding skin and a proprietary boric acid ointment or a dry dressing applied.

Two patients with axillary furunculosis, another with furunculosis of the groin, 2 with furunculosis of the neck and 1 each with furuncles of the ear and leg made rapid and favorable response to this procedure.

Two patients presenting large infected cysts, which were painfully inflamed and swollen, had irrigations with glycerite of hydrogen peroxide following incision and drainage. In both the lesions healed completely within eight days. Three patients in this group merit detailed description. The first, a man aged 53, presented an infected sinus in the scar of a postoperative fractured patella. The scar consisted of six sinus openings, each bathed in pus and filled with granulation tissue. Cultures proved beta hemolytic streptococci, Staphylococcus albus, a few gram-positive cocci and a rare gram-positive bacillus to be present. The sinuses were irrigated twice daily with the solution of glycerite of hydrogen peroxide. Exploration proved the presence of six long, black, silk sutures, which were removed. The infection cleared with the continued irrigation, and the lesion healed within two months.

In the second patient, a man aged 84, contact dermatitis developed on the dorsa of the hands while he was handling brass pipe and a synthetic wool used for packing. A secondary infection occurred associated with lymphangitis and tender epitrochlear and axillary glands, present bilaterally. Deep multilocular abscesses developed in the tissue of the left biceps muscle. Laboratory studies proved Staph. aureus and gram-positive cocci to be present. The patient was hospitalized and the abscesses irrigated with glycerite of hydrogen peroxide, the solution being applied undiluted as a moist dressing between irrigations, which were done twice daily. During the day dressings of isotonic solution of sodium chloride were applied and during the night a proprietary boric acid ointment. Complete recovery occurred in ten days.

The third patient, aged 68, presented at the New England Dermatological Society (February 1945), had suffered for thirty-eight years from chronic liquefying nodular panniculitis of an afebrile type involving the legs. Painful ulcerations occurred in crops, the onset of each lesion being marked by a pink macule 2 to 4 mm. in diameter superimposed on a tender nodule 2 mm. in diameter. These lesions gradually enlarged to form a painful bluishly discolored nodule 2 to 4 cm. in diameter, which eventually broke down with a serosanguinous discharge. Subsequent healing was extremely slow and left a depressed atrophic scar.

Cultures, smears, biopsies and inoculations of a guinea pig failed to reveal any organism, although stained smears demonstrated 14 to 200 leukocytes present in each oil immersion field. The solution of glycerite of hydrogen peroxide used undiluted as an irrigation brought immediate relief from pain and prompt healing of the lesions within ten days, although all previous exacerbations had required three to four weeks for recovery.

PUSTULAR PSORIASIS

In 3 patients with pustular psoriasis affecting the palms, soles, heels, finger nails or scalp, there was no effect following the application of glycerite of hydrogen peroxide.

SOLAR DERMATITIS

In 2 patients who invariably presented pinhead-sized acuminate papules over the cheeks, nose, chin and ears following exposure to the sun, the topical application of glycerite of hydrogen peroxide was ineffective.

SENSITIZATION DERMATITIS

In 4 patients presenting typical sensitization dermatitis on the feet and on the hands, the solution was not effective and actually proved too irritating for continued use.

VERRUCAE

In 10 patients presenting verrucae of the plantar, palmar, periungual and subungual areas, the solution was either applied as a moist dressing constantly for two weeks or at intervals of thirty minutes twice daily or applied to the sheared verrucae at a point at which punctate bleeding occurred. In no instance was the solution effective. In view of the fact that the solution liberates oxygen, it was not injected into the base of any wart.

SUMMARY

The composition and properties of a new antiseptic solution, glycerite of hydrogen peroxide, are described.

Its effects on the cutaneous manifestations of 120 patients, comprising twenty-three clinical entities of the skin and mucous membranes studied over a period of fifteen months, are listed. Since there is at the present no adequate method for making control studies in clinical investigations of this type, we are purposefully limiting our comments to the descriptions of the exact results as recorded in the body of this paper.

The use of the solution in 50 additional patients as a postoperative dressing was marked by an absence of secondary infection.

Although not effective in the treatment of psoriasis, solar dermatitis and verrucae and apparently causing irritation in some cases of tinea barbae and tinea cruris as well as in sensitization dermatitis, it appears effectively to lessen infection and hasten healing time in primary fungous and primary and secondary bacterial infections.

The clinical courses of certain types of virus infections seem favorably influenced by its use.

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EOSINOPHILIC GRANULOMA OF BONE WITH CUTANEOUS MANIFESTATIONS

Report of a Case

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INTEREST of pathologists and orthopedic surgeons has within recent years been focused on a newly classified group of diseases, comprising Hand-Schüller-Christian disease, a relative newcomer, assigned the eponym Letterer-Siwe disease, and a third, variously known as eosinophilic or destructive granuloma of bone. Occurrence of both cutaneous lesions and visceral involvement as prominent accompaniments of these processes recommends further study and investigation by dermatologist and internist.

Letterer-Siwe disease, so titled because of the original description by Letterer and the subsequent collection and grouping of cases by Siwe [1] appears to be the severest, eosinophilic granuloma the mildest and Hand-Schüller-Christian disease the intermediate manifestation of an identical underlying basic disease.[2] This classification necessitates withdrawal of Hand-Schüller-Christian disease from its previously held position in the group known as diseases of lipid metabolism, remaining members of which are Gaucher's disease and Niemann-Pick disease. Recent investigations lend weight to the accuracy of this reshuffling. While the case to be reported is regarded primarily as one of eosinophilic granuloma

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Dr. Cawley is from the service of Dr. U. J. Wile and Dr. A. C. Curtis.

Studies and contributions from the Department of Dermatology and Syphilology, University of Michigan Medical School.

1. Abt, A. F., and Denenholz, E. J.: Letterer-Siwe's Disease: Splenohepatomegaly Associated with Widespread Hyperplasia of Nonlipoid-Storing Macrophages; Discussion of the So-Called Reticuloendothelioses, Am. J. Dis. Child. **51**:499 (March) 1936.

2. (*a*) Green, W. T.; Farber, S., and McDermott, L. J.: Eosinophilic or Solitary Granuloma of Bone, J. Bone & Joint Surg. **24**:499 (July) 1942. (*b*) Gross, P., and Jacox, H. W.: Eosinophilic Granuloma and Certain Other Reticulo-Endothelial Hyperplasias of Bone: A Comparison of Clinical, Radiologic and Pathologic Features, Am. J. M. Sc. **203**:673 (May) 1942. (*c*) Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone: A Condition Affecting One, Several, or Many Bones, but Apparently Limited to the Skeleton, and Representing the Mildest Clinical Expression of the Peculiar Inflammatory Histiocytosis; also Underlying Letterer-Siwe Disease and Schüller-Christian Disease, Arch. Path. **37**:99 (Feb.) 1944.

of bone with cutaneous manifestations, the interrelationship of the three processes is apparently close, entailing a brief description of Letterer-Siwe disease and Hand-Schüller-Christian disease as well as eosinophilic granuloma.

Occurrence in extremely young persons, usually before the age of 2 or 3, severity of the process and extensive generalized involvement can be predicated for Letterer-Siwe disease. Analysis of 9 cases [1] and reports of others paint a fairly typical picture of this disease. Destructive osseous lesions are frequent, and these apparently have a special predilection for the calvarium.[2c] Most frequently confused with these punched-out defects on roentgenographic study are cysts of the bone, metastatic neoplasm and multiple myeloma. Persistent low grade fever is common, and secondary anemia is present relatively often. Hepatomegaly and splenomegaly, with, in addition, enlargement of lymph nodes, occur almost without exception. Cutaneous manifestations have been described as superficial ulcerations of the skin, petechiae, purpura, ecchymoses and combinations of the last three, the hemorrhagic tendency being apparently most pronounced shortly before death. The course pursued is oftenest acute or semichronic, generally fatal in a matter of weeks to two years, although in some cases the condition apparently becomes definitely chronic and passes into the realm of Hand-Schüller-Christian disease.[2c]

Most thoroughly studied and probably best known of the three conditions, Hand-Schüller-Christian disease may at times bear a decided resemblance, clinically and even from a histologic standpoint, to Letterer-Siwe disease and eosinophilic granuloma of bone. Destructive skeletal lesions are relatively common in conjunction with Hand-Schüller-Christian disease, although in an analysis of 84 previously reported cases, 2 with involvement of the soft tissues, but none with roentgenologic evidence of bony lesions were uncovered.[2b] Complete or partial absence of the textbook triad, which embraces diabetes insipidus and exophthalmos in addition to bony defects of the cranium, has been emphasized by several investigators. Presence of one or more is suggestive, and the occurrence of hepatomegaly and splenomegaly, in addition, places emphasis on this disease as a diagnostic possibility. Retarded physical development is not uncommon. Cutaneous lesions, occurring in approximately one third of the cases, have received special attention on at least one recent occasion. A diffuse petechial efflorescence in association with acute manifestations of the disease, and papules or nodules accompanying chronic forms are apparently encountered most frequently.[3]

3. Lane, C. W., and Smith, M. G.: Cutaneous Manifestations of Chronic (Idiopathic) Lipoidosis (Hand-Schüller-Christian Disease), Arch. Dermat. & Syph. **39**:617 (April) 1939.

Various observers have given the mortality rate as approximating 30 per cent.

Description, discussion and study of eosinophilic granuloma, the third and least severe of this group, have been rather extensive in the past few years. In the preponderance of reported cases the condition has occurred in children and young adults. Complete absence of or a minimum of general manifestations is the rule, although localized symptoms referable to the bony lesions, such as pain and swelling, occur with a fair degree of frequency. The destructive osseous lesions, which may suggest Hand-Schüller-Christian disease, Letterer-Siwe disease, cysts of the bone,

Fig. 1.—Discrete, granulomatous papules with a moist surface as they appeared in the right axilla in the reported case.

malignant growth or multiple myeloma to a roentgenologist, are solitary or multiple, a maximum of twenty-five in 1 case having been reported. Flat bones are involved oftenest.[4] Laboratory studies usually present no significant alteration from the normal, although moderate leukocytosis and at times a peripheral eosinophilia of mild degree may be encountered. Cutaneous manifestations, with the exception of one casual reference,[4] have apparently not previously been reported. Prognosis based on cases hitherto described, appears to be uniformly good, although occur-

4. Farber, S.: The Nature of "Solitary or Eosinophilic Granuloma" of Bone, Am. J. Path. **17**:625 (July) 1941.

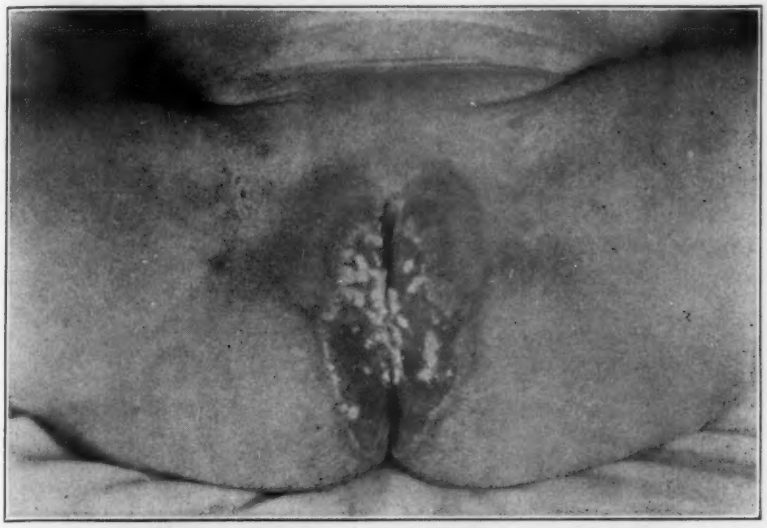

Fig. 2.—Involvement of the vulva and perianal region by a sharply demarcated, erythematous, infiltrated process with a denuded weeping surface.

Fig. 3.—Destructive osseous lesion involving the left ilium. Further roentgenologic examination, subsequent to the administration of roentgen ray therapy, demonstrated complete healing of this as well as other bony lesions.

rence of destructive bony lesions at vital sites [5] may occasion considerable apprehension until the process is controlled. Roentgen therapy, curettage of the osseous lesions or a combination of the two is usually productive of a satisfactory result, and spontaneous healing has been recorded.

As previously described, Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma are believed by most investigators to be individual manifestations of an identical basic process, the exact nature of which has not been determined. One competent observer has expressed the opinion that "a satisfactory working classi-

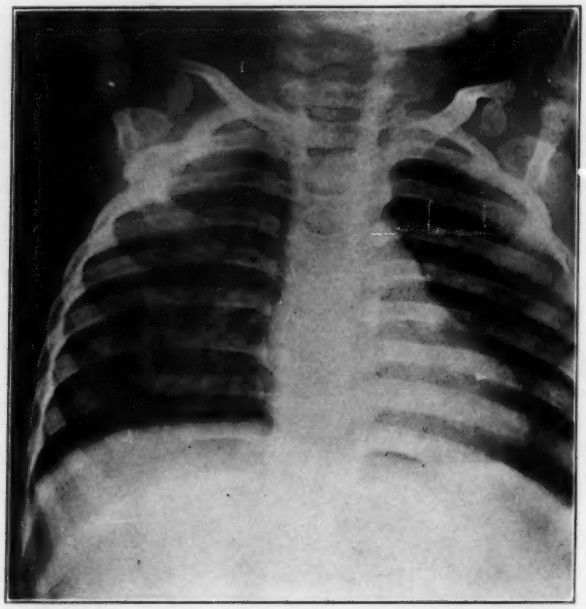

Fig. 4.—Involvement of the axillary portion of the right second rib with a process similar to that in the ilium.

fication of these conditions should include the three separate clinical types of Hand-Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma of bone, with transitional forms between eosinophilic granuloma and each of the other two diseases in this group." [6] The etiologic factor cannot yet be stated, although trauma and possibly infection may play a part. Histopathologic studies of the lesions have probably been most suggestive of the interrelationship of these three condi-

5. Osborne, R. L.; Freis, E. D., and Levin, A. G.: Eosinophilic Granuloma of Bone Presenting Neurologic Signs and Symptoms: Report of a Case, Arch. Neurol. & Psychiat. **51**:452 (May) 1944.

6. Farber, S.: The Nature of Some Diseases Ascribed to Disorders of Lipid Metabolism, Am. J. Dis. Child. **68**:350 (Nov.) 1944.

tions, the findings having been described in detail and in excellent fashion by several of the authors previously cited. Salient points are these: abundance of histiocytes with varying numbers of eosinophils characterize most cases of eosinophilic granuloma, the presence of eosinophils being also at times a feature of Hand-Schüller-Christian disease. Osseous lesions of Letterer-Siwe disease, more particularly early ones, apparently demonstrate infiltration by eosinophils, while lesions of the soft tissue

Fig. 5.—Roentgenologic examination of the skull demonstrated this bony lesion in the vicinity of the antrum, right mastoid.

are said not to present this cytologic picture.[2e] Changes in the bone marrow of various description occur in most cases of Letterer-Siwe disease[1] and are a not uncommon accompaniment of eosinophilic granuloma.

REPORT OF A CASE

In September 1944, G. C., a 16 month old girl from Detroit, was referred to the Dermatology Clinic of the University of Michigan Hospital because of a cutaneous eruption. The child had been as well as usual until the age of 8 months, at which time an eruption similar to seborrheic dermatitis appeared on the scalp.

About the same time, small, red, discrete and coalescent papules became apparent on the buttocks and about the genitalia and erythematous, painful, eroded patches appeared in various parts of the mouth. Shortly thereafter, lesions similar to those on the buttocks and about the genitalia were noted on the soles and between the toes. Despite local therapy the entire process became steadily worse, and the child was seen in the clinic for the first time on Sept. 14, 1944.

The consulting dermatologist described his findings thus: "Over the palate and on the posterior aspect of the tongue are small, grayish white, circumscribed macules. Sharply demarcated, erythematous papules, 2 to 3 cm. in diameter, with a weeping, granulomatous surface are present in each axilla. Over the abdomen and in both inguinal regions are erythematous, scaling papules 1 to 2 mm. in

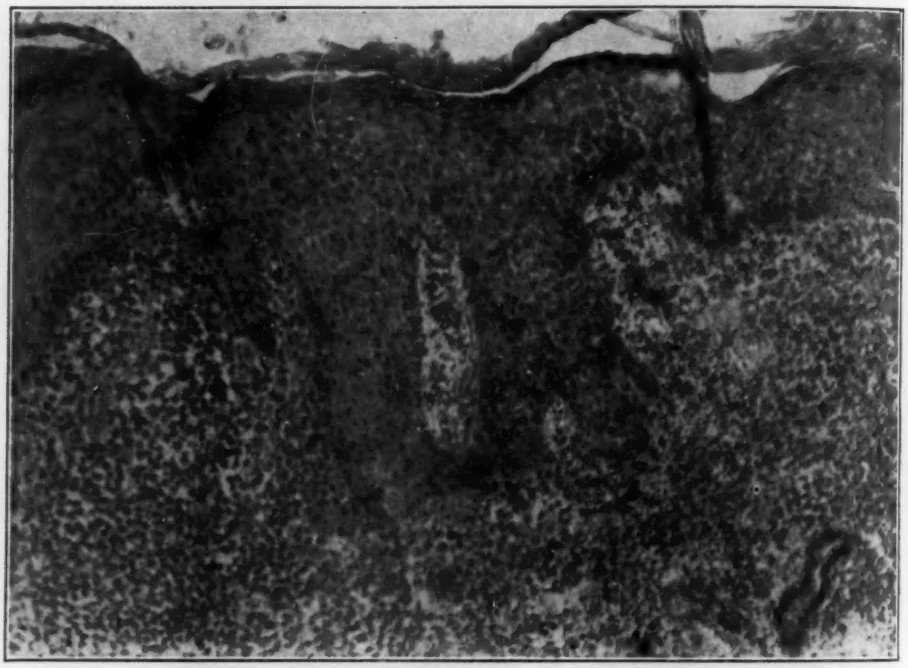

Fig. 6.—Photomicrograph made from a section of one of the cutaneous lesions, showing an infiltrate limited chiefly to the dermis (low power).

diameter, while the genitalia and perianal region are involved by an edematous process with a denuded, weeping surface.

Biopsy specimens were taken from lesions in the right axilla and those on the buttocks and abdomen. Microscopically, all showed the same essential lesion, which at first glance resembled a malignant process, being especially suggestive of reticuloendothelioblastoma. Detailed examination, however, revealed all cells of the infiltrate to be well differentiated, with an abundance of histiocytes and in places a great many eosinophils, a picture compatible with, in the opinion of two authorities,[7] eosinophilic granuloma of bone or Letterer-Siwe disease manifesting cutaneous lesions.

7. Montgomery, H.: Personal communication to the authors. Farber, S.: Personal communication to the authors.

Roentgenologic examination of the skull, chest, long bones and spine demonstrated a destructive lesion involving the axillary portion of the second rib on the right side with an overlying swelling of the soft tissue, in addition to a similar destructive lesion in the left ilium. A similar lesion subsequently developed in the right mastoid. Biopsies of these were not obtained.

During her stay in the hospital the child was not febrile. The liver and spleen were not and did not become palpable, but there were a few small, nontender lymph nodes in both cervical and inguinal regions. A complete blood cell count on several occasions showed no significant alteration from the normal other than a slight toxic granulation of the neutrophils and a sedimentation rate of 27 mm. per hour. No eosinophils were counted. Tibial aspiration was also made. The hematologist reported, "Neither the blood nor the marrow presents definite evidence of neoplastic involvement." The Kahn reaction of the blood was negative, and the urine was normal.

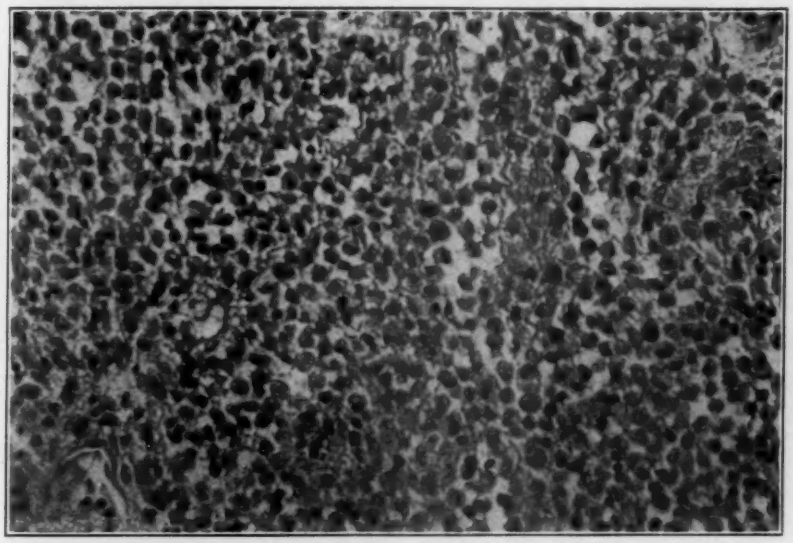

Fig. 7.—High power photomicrograph of the infiltrate shown in figure 6, demonstrating a reticulin containing many histiocytes with varying numbers of interspersed eosinophils.

Following roentgen therapy[8] to the lesions of the bone, as well as to the cutaneous eruption, there was complete but gradual healing, over a period of months, of the former, while the cutaneous manifestations had cleared almost completely at the time the child was last seen. Further skeletal or cutaneous lesions did not occur.

NOTE.—This case was presented and discussed as an example of eosinophilic granuloma of bone with cutaneous manifestations at the annual meeting of the Central States Dermatological Society in Detroit, on April 27, 1946.

8. Five hundred roentgens were delivered to the osseous lesions through 0.5 mm. of copper and 1.9 mm. of aluminum; 300 to 600 r, unfiltered and in divided doses, were delivered to the cutaneous eruption; 1,500 r were delivered to the oral cavity through 0.5 mm. of copper and 1.0 mm. of aluminum, given in divided doses over a period of several months.

SUMMARY

Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma of bone appear to merit classification as closely allied manifestations, varying chiefly in severity, of a basic disease, the exact nature of which is not known. Cutaneous lesions are of frequent occurrence with the first two but have not been described, so far as known, in conjunction with the last. A case presenting findings compatible with a diagnosis of eosinophilic granuloma of bone and demonstrating cutaneous lesions as a part of the process is reported. Roentgen irradiation of both osseous and cutaneous lesions gave satisfactory therapeutic results.

PACHYONYCHIA CONGENITA

Report of Two Cases, with Studies on Therapy

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PACHYONYCHIA congenita is a rare congenital anomaly, originally described under this name by Jadassohn and Lewandowsky.[1] The literature was thoroughly reviewed in 1934 by Diasio,[2] who reported that Heller had previously called attention to the close resemblance between the condition reported by Jadassohn and Lewandowsky and the syndrome described under the caption "congenital dyskeratosis" by Erich Schäfer. Schäfer's observations were based on 1 case of his own and 13 culled from the literature. In 1935 Sohrweide [3] reported a case under the name "pachyonychia ichthyosiformis."

Ormsby [4] in 1943 recognized the title "pachyonychia congenita" and summarized the characteristics as follows:

> dystrophic changes in the nails, palmar and plantar hyperkeratosis, anomalies of the hair, leukoplakia, follicular keratoses of the acne-form type particularly about the knees and elbows and dyskeratosis of the cornea. Verrucous lesions are described as occurring on the knees, elbows, popliteal regions, buttocks, legs and ankles Bullae are common and occur chiefly on the plantar surfaces of the feet. Generalized ichthyosis of variable degree may or may not be present. The affection occurs chiefly with the male sex. In all of the reported cases pachyonychia has been present. All of the associated symptoms above mentioned have occurred in whole or in part in the various cases recorded.

From the Department of Dermatology and Syphilology, Temple University School of Medicine.

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Hot Springs, Va., June 10, 1946.

1. Jadassohn, J., and Lewandowsky, in Neisser, A., and Jacobi, E.: Ikonographia dermatologica, Berlin, Urban & Schwarzenberg, 1907; cited by Diasio.[2]

2. Diasio, F. A.: Pachyonychia Congenita Jadassohn: A Variety of Ichthyosis (Pachyonychia Ichthyosiformis) Inyolving Chiefly the Nails, Arch. Dermat. & Syph. **30**:218-226 (Aug.) 1934.

3. Sohrweide, A. W.: Pachyonychia Congenita: Report of a Case, Arch. Dermat. & Syph. **32**:370-376 (Sept.) 1935.

4. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia Lea & Febiger, 1943.

An excellent description of the microscopic picture of the skin is given by Andrews [5]:

The striking feature of the specimen was a thickening of the epidermis due to acanthosis and parakeratosis, especially pronounced about the pilosebaceous follicles. The rete pegs were lengthened, and about the follicles the epidermal thickening caused funnel-shaped prolongations extending into the corium. The openings of the follicles were dilated and plugged with imperfectly cornified and somewhat degenerated horny material, and horny plugs were also present in the sweat pores. The basal cell layer was irregular and the cells were swollen. There was granular degeneration in the prickle cells; the nuclei stained deeply, and some were crescentic, being pushed to one side of the cell by hydrops. They resembled the *corps ronds* found in cases of Darier's disease. The papillary bodies between the rete pegs were elongated, and in some places the apexes came near the

Fig. 1.—Pachyonychia congenita, showing the thickening of the finger nails and the keratotic lesions of the skin.

surface of the skin. The blood vessels of the corium were dilated and surrounded by lymphocytes, mast cells, connective tissue cells and an occasional plasma cell; the appearance suggested a mild inflammation from the pressure or irritation of the overlying thickened epidermis. The connective tissue seemed normal.

REPORT OF TWO CASES

CASE 1.—I. L., a white boy, was first admitted to the Temple University Hospital in 1936, at the age of 6. At birth the entire cutaneous envelope was rough, and the thumb nails appeared to be "infected." When he was 2 years old "blisters" had formed on the soles, knees and elbows. These ruptured, with the formation of loosely bound crusts. The nails of the hands and feet developed

5. Andrews, G. C.: Pachyonychia Congenita, Arch. Dermat. & Syph. **33**: 183-184 (Jan.) 1936.

abnormally, becoming extremely thick. When the patient was examined at the Temple University Hospital in 1936, a diagnosis of "ectodermal defect" was made and a section of skin submitted to the laboratory. The report on this section was as follows: "Microscopic study revealed small sections of skin showing decided irregularity of the surface with extensive hyperkeratosis. There were small marginations of the surfacce epithelium filled in by horny plugs. The epithelial cells showed dyskeratosis and small areas of parakeratosis. The picture suggested psorospermosis follicularis vegetans of Darier."

Fig. 2.—Thickening of the epidermis due to acanthosis and parakeratosis. The rete pegs are lengthened.

In 1939 the boy was admitted to the Harriet Lane Home for Invalid Children at Johns Hopkins Hospital, with a diagnosis of "chronic eczema secondarily infected, producing an impetiginous picture." The infected lesions were treated with compresses of chlorazodin, potassium permanganate and gentian violet medicinal, after which they healed for a period of six months. New erosive and infected lesions then appeared, and they persisted until the patient was readmitted to Johns Hopkins Hospital in April 1940. In addition to the open lesions the skin at that time was generally rough, and the tongue, gingiva and buccal mucosa

revealed "a diffuse, superficial, leukoplakic involvement." The diagnosis made was "congenital ectodermal dysplasia of as yet unclassified type with secondary infection." At that time the laboratory findings were as follows: hemoglobin content 100 per cent; white blood cells 10,000; differential count normal; urine normal; serum protein content 5.9 Gm. per hundred cubic centimeters; albumin-globulin ratio 1.3; serum cholesterol level 161 mg.; results of roentgenologic examination of the gastrointestinal tract normal; scrapings of the skin negative for fungi; blood Wassermann reaction negative, and tuberculin reaction (to 0.1 mg.) negative.

In June 1942 the boy was readmitted to the Temple University Hospital for further study, and between that date and June 1945 there was a total of six admissions, varying in length from a few days to several weeks. Observations at examination in 1942 were as follows: "The skin was generally dry and thick-

Fig. 3.—Pachyonychia congenita, illustrating crusted cutaneous lesions and thickening of the toe nails.

ened, with many elevated lesions resembling keratotic plugs, particularly over the shoulders, elbows and knees. The feet had denuded, crusted patches extending from the soles up the medial and lateral aspects. Removal of the crusts revealed reddened bases having a shiny or somewhat glazed appearance. The hair was dry and lusterless. The buccal mucosa and tongue showed patches suggestive of leukoplakia. Most striking were the changes in the nails. The nails of the hands and feet were greatly thickened, some to a depth of ½ inch (1.2 cm.). The growth of the nail appeared to be away from the nail matrix rather than from the nail root."

The boy and his parents were chiefly interested in therapy for the crusted inflammatory patches and the nails. Because of the overgrowth of the nail plate he was able to make but little use of his fingers. Wet dressings of buffered

cysteine hydrochloride, as described by Goldberg,[6] were continuously applied to the crusted areas, and within ten days all lesions were healed. (It is worthy to note that during subsequent recurrent outbreaks of these inflammatory crusted lesions various other applications were tried, but invariably it was necessary to use the buffered cysteine hydrochloride to bring about healing.)

A consultation with a member of the surgical staff, Dr. George Rosemond, was requested, and the decision was reached to remove the nail plates completely with the patient under general anesthesia. This was done Nov. 17, 1942 and the patient sent home. In June 1943 the patient returned, showing only a partial return of the thickening of the nail plates but with recurrent erosive and crusted lesions on the feet. These again cleared completely with wet dressings of buffered cysteine hydrochloride solution.

In October 1944 the patient returned, showing regrowth of all the nails to about one half of their original thickness. As it was realized that the only method of completely stopping the growth of the nail would mean complete removal of the matrix, which in the condition is apparently the root from which

Fig. 4.—One of the removed finger tips, showing the upward growth of the nail.

the nail grows, it was decided in consultation with Dr. Rosemond to remove completely the tip of one finger as a trial method of therapeusis. Obviously such a procedure would result in a finger completely lacking a nail.

The next admission to the hospital was in February 1945, and this time the boy requested that the same procedure of removing the distal phalanges be used for all the fingers and the thumb of the right hand, as he had had no discomfort in the one finger and could use it for the first time in his life. The operation was performed with the patient under general anesthesia. In June 1945 the same procedure was followed with the left hand, the operation having been almost completely successful on the right hand. Apparently a small amount of matrix was not removed from the middle finger, and it resulted in a slight regrowth of the nail. The final result of the operations may be seen in figure 5. Microscopic study of the distal phalanges, including the structure of the nails, was impossible

6. Goldberg, L. C.: Resistant Erosive Lesions in Pachyonychia Congenita of Jadassohn: Treatment with Buffered Cysteine Hydrochloride, Arch. Dermat. & Syph. **36**:331-334 (Aug.) 1937.

because of lack of a satisfactory method of softening the nail sufficiently to permit cutting with the microtome.

A biopsy of tissue from one of the crusted inflammatory denuded patches resulted in the following report: "The tissue consists of an outer thick layer of keratin material which has a laminated appearance. It contains numerous pyknotic nuclei. Below this is a layer of stratified squamous epithelium which is moderately acanthotic. It has a pseudopapillary arrangement. Its rete pegs are disorderly. The corium shows fibrous thickening and adenomatoid hyperplasia. The histologic picture could be that of a clavus or pachyderma."

The second case has not been studied as intensively, nor has it been possible to keep the patient under as close observation as the patient in case 1, but it is included chiefly because of the extreme early age at which the patient was first seen.

Fig. 5.—Appearance of the hands one year after removal of distal phalanges.

CASE 2.—T. N., a 5 month old infant girl, was seen in consultation in February 1942. The entire skin was dry, with some papular accentuation of the follicles, particularly on the extensor surfaces. On the trunk were two small irregular hemangiomas of the strawberry mark type. The nails were all greatly thickened, with the excessive growth away from the nail matrix rather than away from the tip of the nail plate. The mucous membranes showed several superficial white patches, which had been diagnosed and treated by a pediatrician as "thrush." The case was presented to the Philadelphia Dermatological Society as a typical case of pachyonychia congenita. Treatment consisted in (1) application of solid carbon dioxide to the nevi, (2) administration of massive doses of vitamin A and (3) local application of a mild emolient.

COMMENT

In addition to adding 2 cases of this rare congenital anomaly to the literature, our interest was directed to the question of therapy. There are three phases of pachyonychia congenita that distress the affected

person: (1) the dry hyperkeratotic skin with acneform follicular keratoses; (2) the bullous and crusted lesions that appear from time to time, chiefly on the feet, and (3) the greatly thickened nails.

We found that the dry skin could be kept in a comfortable state by massive doses (100,000 units daily or more) of vitamin A, infrequent bathing and the use of an emollient.

At the Harriet Lane Hospital for Invalid Children (Johns Hopkins Hospital) the bullous and crusted lesions in case 1 were reported to have healed after treatment with compresses of chlorazodin, potassium permanganate dressings and gentian violet medicinal. It was not made clear which of these agents had proved most effective. At the Temple University Hospital various local applications were employed, including boric acid solution, wet dressings and a modified ichthammol ointment, but until wet dressings of a buffered solution of cysteine hydrochloride, as suggested by Goldberg,[6] were employed the results were discouraging. As described in case 1 the latter solution invariably healed the open lesions in from ten days to two weeks. Recurrence within a few weeks after application of the cysteine hydrochloride dressings was stopped was invariably the rule.

The cause of the greatest discomfort to the boy described in case 1 was the dystrophic finger nails, which rendered his fingers virtually useless. Removal of the nail plates proved ineffective, as regrowth was rapid. This is similar to Andrews'[5] experience, for in a case reported by him removal of the nails by a surgeon was followed by "regrowth in a distorted fashion."

Careful study of the growth of the nails in pachyonychia congenita indicates that growth is away from the matrix of the nail rather than from the root of the nail. Thus the only successful therapy consists in complete removal not only of the plate but of the matrix as well, which in these cases is identical with the root or origin of growth. Complete removal of the distal phalanges of the fingers and thumbs in 1 of our cases resulted in giving the patient useful fingers. This is forcefully illustrated by the fact that he is now taking piano lessons and has free use of the fingers in spite of the radical surgical procedure.

SUMMARY

1. Two cases of pachyonychia congenita are reported with clinical and laboratory findings.

2. Studies of therapy indicate that (*a*) the dry keratotic skin may be improved by massive doses of vitamin A and emollients; (*b*) the use of wet dressings of buffered cysteine hydrochloride, as suggested by Goldberg, will temporarily heal the bullous and crusted lesions, and (*c*) removal of the distal phalanges of the digits is the only way to free the fingers of the distorted dystrophic nails and make them useful.

ABSTRACT OF DISCUSSION

DR. HAROLD COLE, Cleveland: The patient in the original case of Jadassohn and Lewandowsky was a girl 15 years old, and she had a brother aged 4. Her nails were thick and folded longitudinally and assumed a conelike surface, such as is shown in these pictures, while the great toe nails assumed somewhat the character of onychogryposis, which is well brought out in this boy. The girl had hyperhidrosis of the nose, and there were patches of reddish papules on the nose with fine watery blisters. In the summer the girl had bullous lesions on the soles, just exactly the same as this patient had, while both she and her brother had over the knees and elbows millet seed–sized papules, capped with a horny center, which on removal left a bleeding spot; this shows up well on this patient. The patient also had lesions over the scapulas on the anterior and posterior axillary folds that were similar to this. The tongue of the girl showed extensive leukokeratosis but not leukoplakia. The tissues were really piled up. There is a distinction.

Kumer and Loos (*Wien. klin. Wchnschr.* **48**:174, 1935) attempted to assemble some of these related dermatoses. In one form there was a symmetric volar dermatosis with follicular keratoses of the body; in the second, there were keratoses of the hands or feet or both with leukokeratoses of the mouth and even of the vocal cords, i. e., the so-called Riehl type, and third, there were the aforementioned changes along with the corneal alteration. The process is dominant and is hereditary. Some of the patients have the loss of hair, hyperhidrosis, formation of bullae and onychogryposis.

The condition in the male patient seen by Rauschkolb, Toomey and Cole (ARCH. DERMAT. & SYPH. **27**:71 [Jan.] 1930) and a counterpart more recently reported from Fred Wise's service by Garb and Rubin differed from pachyonychia congenita in that there was a dystrophy of the nails. In our case the patient has a true leukokeratosis in the mouth but no involvement of the larynx.

I was much interested in this report, and these cases certainly are extremely similar, outside of the dystrophy of the nails in the one instance as compared with the pachyonychia congenita that Jadassohn names in the other condition.

DR. FRED WISE, New York: Two brothers with pachyonychia congenita treated by Dr. Garb at the Skin and Cancer Unit of the New York Post-Graduate Medical School Hospital with testosterone propionate showed considerable improvement. One of the brothers suffered from advanced leukokeratosis of the tongue and buccal mucosa, dystrophy of the nails, alopecia and hyperpigmentation of the neck and face, together with signs of hormonal deficiencies. The leukokeratosis responded favorably but showed a tendency toward recurrence when the medication was discontinued. Gain in weight and improvement of the general health of the patient were notable while the treatment was administered regularly.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Dr. Ormsby and I have had difficulty in trying to group and classify some of these congenital ectodermal and mesodermal defects, and, in connection with the cases that Dr. Cole mentioned that he has reported, I should like to call attention to an article by Dr. Thannhauser on "Werner's Syndrome (Progeria of the Adult) and Rothmund's Syndrome: Two Types of Closely Related Heredofamilial Atrophic Dermatoses with Juvenile Cataracts and Endocrine Features" (*Ann. Int. Med.* **23**:559-626, 1945). I believe that there are too many names for varying diseases that are related, and I hope that some one will straighten out this subject. It is true that there are typical cases of pachyonychia congenita, and I do not question the diagnosis as presented.

DR. JOHN G. DOWNING, Boston: Dr. Wise's remarks prompt me to describe a patient whom I saw June 24, 1944, a boy aged 16 years with a more or less generalized cutaneous disturbance. He had keratotic papules on his arms, legs and body, with bullous lesions on the hands and feet. There were paronychial lesions on most of the fingers, with changes in the nails consisting of ridges and subungual hyperkeratosis. I thought that he had a vitamin A deficiency, but he showed little improvement with large doses of vitamin A. He was later seen by an endocrinologist, who prescribed androgens 2.9 mg., a total of 17-keto steroids per twenty-four hours, and estrogens 3.6 mg., a total of 17-keto steroids per twenty-four hours. Under this therapy his cutaneous lesions were relieved, and at the last report, three months ago, he was still well.

DR. CARROLL S. WRIGHT, Philadelphia: I appreciate the discussions. I really do not think that there is anything more that I can add. I agree that there is a great deal of confusion about this subject, but, if any one takes the trouble to look up the reported cases of pachyonychia congenita with which there are photographs, it will be seen that they all look just like this case; I think that this is a distinct type of congenital defect which probably deserves the term that it has been given.

LONGITUDINAL GROOVING OF THE NAILS CAUSED BY SYNOVIAL LESIONS

C. RUSSELL ANDERSON, M.D.
BEVERLY HILLS, CALIF.

IN 1942 Eliassow and Frank [1] contributed an excellent review of the literature on synovial lesions of the skin. They also demonstrated incontrovertibly the connection of the synovial lesions with adjacent joint cavities by aspirating a synovial lesion and then replacing the aspirated fluid with diodrast (Winthrop Chemical Company, Inc.; 3, 5-diiodo-4-pyridone-N-acetic acid and diethanolamine [35 per cent weight per volume]). The roentgenogram taken immediately after the injection showed the contrast medium in the synovial lesion and in the adjacent joint itself. The authors offered the concept that synovial lesions of the skin were due to an escape of synovial fluid from the joint cavity.

The genesis of synovial lesions has never been satisfactorily explained. Ormsby [2] suggested an arthritic diathesis. Jensen [3] offered the concept that the synovial lesions had "their origin in embryonic arrests in the process of the development of periarticular tissue and synovial membranes." In 1937 Gross [4] stated his belief that the synovial cysts were the result of a peculiar mucoid degenerative change in the connective tissue of the corium, leading to liquefaction and cyst formation, and considered local injuries and thrombosis of small arterial channels as likely causes of this degeneration. I believe that synovial lesions appear as degenerative manifestations of the latter half of life, inasmuch as I have always seen them associated with some degree of hypertrophic arthritis of the terminal interphalangeal joints and never before the age of 40.

During the past ten years I have seen a large number of synovial lesions, but not until the past year have I seen a peculiar longitudinal grooving of the nails due to these synovial lesions, nor have I found it described anywhere. Fordyce [5] reported 3 cases in which cysts were present on the terminal phalanges of the fingers near the base of the nail,

1. Eliassow, A., and Frank, S. B.: Pathogenesis of Synovial Lesions of the Skin, Arch. Dermat. & Syph. **46**:691 (Nov.) 1942.

2. Ormsby, O. S.: Synovial Lesions of the Skin, J. Cutan. Dis. **31**:943, 1913.

3. Jensen, D. R.: Ganglia and Synovial Cysts: Their Pathogenesis and Treatment, Ann. Surg. **105**:592 (April) 1937.

4. Gross, R. E.: Recurring Myxomatous, Cutaneous Cysts of the Fingers and Toes, Surg., Gynec. & Obst. **65**:289 (Sept.) 1937.

5. Fordyce, J. A.: Nail Cysts, J. Cutan. Dis. **36**:589 (Dec.) 1918.

but he did not describe any changes in the nails. In his book, Pardo-Castello [6] referred to Fordyce's article but did not mention changes in the nails secondary to synovial lesions.

My first patient presented a lateral longitudinal grooving of the nail on the fifth finger of the left hand, without any evidence of cyst formation but with a complaint of tenderness of the nail root just proximal to the grooving of the nail. After three weeks she returned and told me that a small amount of clear viscid fluid had been expressed from under the fold of the nail near the longitudinal grooving, giving relief from tenderness of this area. I was able to express a small amount of this fluid, and I made a diagnosis of supraungual synovial lesion.

A, synovial lesion of the right third finger. *B*, longitudinal grooving of the nail on the index finger of the left hand.

My second patient presented a synovial lesion of the dorsal surface of the distal interphalangeal joint of the third finger of the right hand (fig., *A*) and a longitudinal grooving of the radial side of the nail on the index finger of the left hand (fig., *B*), both lesions having been present for six months. At this time there was no visible evidence of a synovial lesion associated with the longitudinal grooving of the nail, but the patient did complain of a slight degree of tenderness on pressure over the adjacent fold of the nail. Two weeks later there was a sudden increase of tenderness, and a tense swelling of the skin appeared over

6. Pardo-Castello, V.: Diseases of the Nails, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 58.

the root of the nail on the index finger of the left hand, just proximal to the grooving, as shown in the illustration (fig., *B*). After appropriate roentgen therapy, this cyst disappeared and the nail recovered its former normal contour. I have seen several other similar cases.

The diagnosis is simple when there is visible evidence of a cystic lesion on the same or other fingers. However, this longitudinal grooving of the nail may be present for as long as six months before a visible associated cystic lesion appears. Its presence in a person over 40 years of age should lead one to consider the existence of a synovial lesion lying over the nail root and disturbing the growth of the nail.

SUMMARY

Longitudinal grooving of the nail plate due to the presence of a supraungual synovial lesion in the region of the nail root is described for the first time. The genesis of synovial lesions is discussed.

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News and Comment

GENERAL NEWS

Rocky Mountain Dermatologic Society Formed.—On Jan. 31, 1947 a group of dermatologists practicing in the Rocky Mountain region met in Denver for the purpose of discussing the formation of a dermatologic society for that region. The dermatologists in Denver had met at a previous date, establishing a temporary organization to prepare plans for the initial meeting.

The meeting began with the presentation of cases at the University of Colorado School of Medicine and Hospitals. Following the clinical portion of the meeting, a business session was held. The expressions of those gathered unanimously favored the formation of such a society for this area. A permanent organization was established, a constitution adopted, officers elected and the name Rocky Mountain Dermatologic Society accepted. Meetings will be held at least twice yearly. There are eighteen charter members, practicing in Denver, Colorado Springs, Colo., Pueblo, Colo., Salt Lake City and Albuquerque, N. M.

American Board of Dermatology and Syphilology.—At the meeting of the American Board of Dermatology and Syphilology, Inc., in New York, April 25, 26 and 27, 1947, the following thirty-eight candidates were voted certificates, and they may now be referred to as certified specialists: Harold E. Anderson, Long Beach, Calif.; Paul Prince Boswell, Chicago; William Cohen, Trenton, N. J.; Charles J. Courville, Detroit; Will Charles Davis, Portland, Ore.; David J. Dolan, Brooklyn; Lemuel Price Ereaux, Montreal, Canada; Benjamin David Erger, Brooklyn; Alfred B. Falk, Chicago; Merriam G. Fredericks, Duluth, Minn.; Abraham J. Gewirtz, Brooklyn; Alexander Gregor Gradow, San Francisco; Meyer Hantman, Cleveland Heights, Ohio; Joseph M. Hitch, Raleigh, N. C.; William McPherson Huber, New York; David Kahn, Lansing, Mich.; William Henry Kaufman, Charlottesville, Va.; Joseph V. Kennedy, Washington, D. C.; Charles Walter Knerler, Oklahoma City; Max Elliott Krause, Oakland, Calif.; Georges Leclerc, Montreal, Canada; Morris Leider, Brooklyn; Milton E. Lowell, Westfield, N. J.; Columbus Hal McCuistion, Austin, Texas; James A. McGuire, Denver; Frederick R. Mebel, Rockville Center, Long Island, N. Y.; Rafael Rivera, New York; Walter Felix Rosenberg, Hempstead, Long Island, N. Y.; Gdali Rubin, Brooklyn; David Mitchell Sidlick, Philadelphia; John Clark Slaughter Jr., Ann Arbor, Mich.; Harry R. Staley, Kansas City, Mo.; Howard Paul Steiger, Philadelphia; Gustav Weissberg, New York; John Francis Wilson, Philadelphia; Eliot Wolk, Studio City, Calif.; George Joseph Zippin, New York, and Isadore Zugerman, Philadelphia.

The following eight candidates were also successful in the examinations and will become certified specialists when they have fulfilled the requirement of five years of training and experience in the specialty: Edward Hunter Boggs, Charleston, W. Va.; Marcus B. Einhorn, Albany, N. Y.; Zachary Felsher, Chicago; Phyllis E. Jones, Oklahoma City; Rose B. Saperstein, New York; Arthur Louis Shapiro, Chicago; Evelyn G. Wallace, Hot Springs, Ark., and Herschel Selig Zackheim, Detroit.

Abstracts from Current Literature

STEVENS-JOHNSON SYNDROME (ERUPTIVE FEVER WITH STOMATITIS AND CONJUNCTIVITIS). SIMON KOVE, Am. J. M. Sc. **210**:611 (Nov.) 1945.

The author describes 2 cases of Stevens-Johnson syndrome, whose clinical course is characterized by the acute onset of fever and prostration, associated with a cutaneous eruption, severe membranous stomatitis and purulent conjunctivitis. A macular-papular or vesicular eruption, which varies in severity in individual cases, may be present. The course usually lasts about two to three weeks and may be followed by a recurrence. Though he states that "Certainly this syndrome differs from erythema exudativum multiforme," several of the excellent photographs represent eruptions which most dermatologists would readily diagnose as erythema multiforme. Thus there remains some question whether the titles "Stevens-Johnson syndrome" or "eruptive fever with stomatitis and ophthalmia" are any more suitable than erythema multiforme.

INFECTIOUS MONONUCLEOSIS: AN ANALYSIS OF 26 CLINICAL AND 340 SUBCLINICAL CASES. RAY VANDER MEER, CHARLES H. LUTTERLOH and JEAN PILOT, Am. J. M. Sc. **210**:765 (Dec.) 1945.

The authors observed a series of 356 patients whom they thought had infectious mononucleosis. The study is of a broad nature, giving particular consideration to subclinical cases. Of greater dermatologic interest are the 18 typical cases in 8, of which (30 per cent) an eruption was present. In 2 of these it was practically indistinguishable from the typical rash seen in measles, and in a third it appeared more like the usual manifestation in early scarlet fever. It is noted that other observers have recorded purpuric, vesicular and urticarial eruptions and that some eruptions are practically indistinguishable from German measles.

THE USE OF A HISTAMINE ANTAGONIST, BETA-DIMETHYLAMINETHYL BENZHYDRYL ETHER HYDROCHLORIDE, IN ALLERGIC DISEASE. ALEX S. FRIEDLAENDER, Am. J. M. Sc. **212**:185 (Aug.) 1946.

Friedlaender reports on the results of use of Benadryl (beta dimethylaminoethyl benzhydryl ether hydrochloride) in a group of 47 patients with a variety of allergic complaints. Of the patients with urticaria all had some degree of relief, and Friedlaender regards the drug as the most effective agent yet used as a palliative measure. Of 4 patients with atopic eczema 2 had decided reduction of pruritus after taking the drug.

Sixteen of the 47 patients complained of some side effects following use of the drug. The commonest symptoms were drowsiness, dizziness, weakness, faintness, fatigue and gastrointestinal upsets.

CAPILLARY MICROSCOPY, WITH SPECIAL REFERENCE TO CAPILLARY PETECHIAE. ELI DAVIS, Am. J. M. Sc. **212**:192 (Aug.) 1946.

Using a standard binocular microscope, Davis examined the finger nail beds of over 1,000 patients. He points out that the capillary pattern of any person is usually consistent. While variations are observed frequently, he states the belief that unwarranted inferences have been drawn from those variations which are well within normal. He states that he has not yet seen capillary petechiae in a healthy person, though many patients showed such lesions when no cutaneous petechiae were seen. No type of petechia was pathognomonic of any disease. One hundred patients with petechiae were found among 533 consecutive patients examined by capillary microscopy. Among these patients were 3 of 13 patients with syphilis and 4 of 7 patients with Raynaud's disease.

CLINICAL AND LABORATORY STUDIES OF LIVER FUNCTION IN THERAPEUTIC MALARIA. PAUL M. GLENN, LAWRENCE I. KAPLAN, HILTON S. READ and FREDERIC T. BECKER, Am. J. M. Sc. **212**:197 (Aug.) 1946.

The authors report the results of investigation of a group of 60 patients inoculated with malaria. They conclude that the liver is involved in every case of malaria, showing some degree of dysfunction by various tests. In most instances the involvement is not severe, since the tests of hepatic function show a return to normal in a short period. The results of cephalin cholesterol flocculation test return to normal more slowly. Their patients were divided in three groups, depending on the diet and on the dietary supplements given. Clinical jaundice appeared about equally in all three groups. There was no correlation between the observation of jaundice and the palpability of the liver. Enlargement of the liver was found less frequently among patients who were given 75 Gm. of dextrose intravenously daily. Tests of hepatic function failed to show any protection of the liver by the addition of protein to the diet, high vitamin intake or injections of crude liver extract. The authors conclude that the digestive symptoms experienced during malaria therapy are not dependent on the hepatic disease but largely on the malaria and perhaps the fever itself.

AN ACCOUNT OF STOCK. REGINALD FITZ, Arch. Int. Med. **76**:210 (Oct.) 1945.

Many physicians have expressed the opinion that there has developed in the medical profession an ominous liability to coronary thrombosis or other manifestation of vascular disease. Fitz has studied the problem by investigating the obituary columns of *The Journal of the American Medical Association* and comparing the data with several statistical surveys, arriving at several interesting conclusions. Year by year, fewer physicians under 60 years of age are dying, and more are living to attain 70 and 80 year marks since the total number of physicians living to pass the age of 60 has increased steadily. Vascular disease is now encountered commonly as a cause of death among physicians at all ages and is increasing in frequency.

There has been a satisfactory diminution in the relative number of deaths from all causes and among all ages, especially notable among those under 40 but perceptible among those over 60. Physicians differ little from the rest of the citizens of the United States in respect to the causes of their deaths at different ages though physicians up to the age of 60 are somewhat protected as a class; considerably few of them, for example, die of accidents and tuberculosis and their specific death rate from all causes is lower. Physicians past 50 appear to have proportionately more fatal cerebral vascular accidents and a slightly higher death rate from all causes. If deaths from cardiac, renal and cerebral vascular disease are grouped, physicians between 40 and 60 years of age appear to die a little more commonly from these causes than do members of the general white male population, probably because they have a better chance of avoiding death from other insults. Fitz concludes that so long as physicians continue to improve their methods and to build up a profession whose members grow steadily older in years and larger in numbers, the mortality rate from vascular disease will increase.

SICKLE CELL ANEMIA IN WHITE PATIENTS WITH ULCERS OF THE ANKLES: REPORT OF TWO CASES. A. C. WOOFTER, WILLIAM S. DICK and WALTER L. BIERRING, Arch. Int. Med. **76**:230 (Oct.) 1945.

Quoting authoritative reports, Woofter, Dick and Bierring state that sickle cell anemia can occur in white persons. They describe a family without known negroid influences but with a brother and sister having characteristic anemia and ulcers of the ankles. Their grandmother had pallor and ulcers of the ankles, a father and uncle were pale and had recurrent ulcerations since childhood; one brother had delayed sickling, and another brother was apparently normal.

LYNCH, St. Paul.

TUMOR OF TACTILE END ORGANS. JAN CAMMERMEYER, Arch. Path. **42**:1 (July) 1946.

Cammermeyer describes an unusual tumor which contained well developed tactile corpuscles but did not give any subjective sensation to the patient. It contained multiple tactile end organs or corpuscles and showed great variations in the number of nerves, their course and their caliber. The specific portion of the tumor was surrounded by a mass of connective tissue. The author states the belief that the tumor may have developed because of faulty organization of embryonal tissue, as has been theorized in the case of other neurogenic tumors.

ANGIOMATOID FORMATIONS IN THE GENITAL ORGANS WITH AND WITHOUT TUMOR FORMATION. ROBERT P. MOREHEAD, Arch. Path. **42**:56 (July) 1946.

Morehead points out that in recent years a group of neoplasms have been noted in the genital tract which possess an unusual but characteristic morphologic picture. He points out that the lesions under consideration are composed primarily of two structural units, namely (1) fibromuscular tissue of the type which ordinarily composes myoma and (2) groups of cells which are predominantly angiomatoid in arrangement and are intermingled with cells structurally resembling small lymphocytes. After studying the available cases he expresses the opinion that the data strongly support the hypothesis that angiomatoid tissue is derived from mesenchymal cells which make imperfect attempts at the formation of lymph vessels and lymphocytes.

HEPAR LOBATUM: CLINICAL SIGNIFICANCE OF THE ANATOMIC CHANGES. DOUGLAS SYMMERS and DAVID M. SPAIN, Arch. Path. **42**:64 (July) 1946.

The authors state that over a period of thirty years hepar lobatum was encountered 102 times among 23,792 necropsies at Bellevue Hospital. According to the clinical records of 28 cases that were available for analysis, the lesion occurred 23 times in men and 5 times in women; 24 patients were of the white race and 4 were Negroes. The average age was 38.5 years; the youngest patient was 19 and the oldest 80. Six patients admitted excessive use of alcohol. The diagnosis of syphilitic cirrhosis of the liver was made during life in 3 cases, and the disease was suspected in 1. Clinical records were available for analysis in 28 cases, in only 4 of which had the diagnosis been suspected or made during life. In most instances the liver was palpable, and in half the cases the spleen was palpable. Jaundice occurred in 8 cases, ascites in 18 and hematemesis in 7. An irregular temperature was present in 12 cases. Symmers and Spain state that the clinical diagnosis of hepar lobatum is dependent almost exclusively on physical signs rather than symptoms. They express the opinion that in attempting a clinical diagnosis confirmatory evidence should be sought in the form of response to treatment and consideration should be given to the advisability of biopsy.

BIREFRINGENCE IN TISSUES. A. L. LICHTMAN and JOHN R. MCDONALD, Arch. Path. **42**:69 (July) 1946.

Double refraction of light by biologic substances is a reflection of the fundamental structure of tissues. Three types of birefringence in tissues have previously been described. The author briefly discusses the changes which have been observed in hair, nail and horn. He also points out that microscopy with polarized light aids in distinguishing between granulomas produced by bacteria and those produced by viruses. He also notes that study of the cholesterol esters aids in the interpretation of various inflammatory processes. He expresses the belief that further benefits are to be gained by the use of the polarizing microscope in pathology.

TREATMENT OF POST-TRAUMATIC SIMMONDS' DISEASE WITH METHYL TESTOSTERONE LINGUETS. H. LISSER and L. E. CURTIS, J. Clin. Endocrinol. **5**:363 (Nov.) 1945.

Lisser and Curtis describe a 20 year old man whose panhypopituitarism followed fracture of the skull. Among the signs of the disease were progressive loss of

facial and body hair (the scalp hair remained normal), loss of libido and potentia, increasing fatigability, and the skin acquired a fawn color. In the course of nine months' treatment with methyl testosterone linguets, the sexual hair reappeared and there was general recovery.

CHRONIC IDIOPATHIC HYPOPARATHYROIDISM WITH SUPERIMPOSED ADDISON'S DISEASE IN A CHILD. MARTHA F. LEONARD, J. Clin. Endocrinol. **6**:493 (July) 1946.

ADENOCORTICAL CANCER WITH UNDULATING FEVER IN ADDISON'S DISEASE. A. P. CAWADIAS, ibid. **6**:507 (July) 1946.

ADDISON'S DISEASE IN AN INFANT. J. C. JAUDON, ibid. **6**:558 (Aug.) 1946.

These individual reports are of interest because they do not describe the usual aspects of Addison's disease. Leonard reports the rare occurrence of combined parathyroid and adrenal insufficiency. The hypoparathyroidism began at about 3 years, and the Addisonian pigmentation appeared at about 10 years. Necropsy established almost complete absence of adrenocortical tissue and no demonstrable parathyroid tissue.

Cawadias reports an instance of Addison's disease caused by adrenocortical carcinoma, and he expresses the opinion that this association may not be so rare as is generally thought. The author also gives consideration to the presence of fever and to psychologic manifestations in Addison's disease.

Jaudon reports an instance in which Addison's disease began in the first year of life and followed the usual course. In this case it was thought that tuberculosis was the etiologic agent responsible for hypofunction of the adrenal cortex.

LYNCH, St. Paul.

LICHENOID DERMATITIS. EUGENE S. BERESTON, J. Invest. Dermat. **7**:69 (April) 1946.

The author presents his observation of 200 cases of so-called lichenoid dermatitis, a chronic dermatosis which occurred among personnel stationed in the South Pacific area and other areas where quinacrine hydrochloride was administered in relatively large amounts over long periods.

Three distinct clinical types of lesions were observed. The eczematoid type was the commonest and usually involved the dorsal surfaces of the extremities. The lichen planus–like type often involved the entire body, including the mucous membranes. The mixed type consisted of eczematoid and lichen planus–like lesions occurring in the same person. All three types often changed into an exfoliative dermatitis of serious proportions.

The histopathologic picture chiefly resembled that in lichen planus, although some characteristics of psoriasis were also present.

The prognosis for cure of the acute lesions is excellent provided the patient is evacuated from the tropics.

A COMBINATION TREATMENT FOR LICE AND SCABIES. GAINES W. EDDY, J. Invest. Dermat. **7**:85 (April) 1946.

The author, a member of the Department of Agriculture, presents a formula designated as N. B. I. N., consisting of benzyl benzoate (68 parts), Tween 80 (14 parts), benzocaine (12 parts) and DDT (dichlorodiphenyltrichloroethane) (6 parts), for the treatment of pediculosis capitis, Phthirus pubis and scabies.

It is claimed that this formula is nontoxic and nonirritating, can be applied safely to the more tender areas of the body and is highly effective not only against the parasites but also against their eggs.

SCABIES AND PEDICULOSIS TREATED WITH BENZYL BENZOATE, D. D. T. BENZOCAINE EMULSION. CEDRIC C. CARPENTER, JOHN A. HEINLEIN, MARION B. SULZBERGER and RUDOLF L. BAER, J. Invest. Dermat. **7**:93 (April) 1946.

An analysis is presented of the various methods for the treatment of scabies used at the United States Naval Hospital, Brooklyn.

The sulfur treatment required an average hospitalization period of ten days and produced a high incidence of secondary dermatitis.

The treatment with benzyl benzoate was found to be an improvement over all former methods and reduced the patients' stay in the hospital to five and one-half days. The incidence of irritations was less frequent provided the treatment could be limited to one or two applications.

The formula N. B. I. N. (benzyl benzoate, DDT and benzocaine emulsion) was found so satisfactory that no hospitalization was required, and one to four sprayings produced permanent cures in 41 of 42 patients. A single application was also effective in curing 15 patients with pediculosis pubis and 4 patients with pediculosis capitis.

Although no evidence of toxicity developed in this series from N. B. I. N the authors warn that further studies are required to confirm the lack of toxicity of DDT (dichlorodiphenyltrichloroethane) present in this formula.

STUDIES IN HYPERSENSITIVITY TO LIGHT. HAROLD F. BLUM, RUDOLF L. BAER and MARION B. SULZBERGER, J. Invest. Dermat. **7**:99 (April) 1946.

Studies on wavelength in a case of urticaria solaris showed that lesions were produced by wavelengths shorter than 3,700 angstrom units. The authors suggest that this condition be designated as urticaria solaris (wavelength less than 3,700 angstrom units) and should be regarded as a distinct etiologic entity.

Through passive transfer tests photosensitivity was induced by the same wavelength in normal skin. It is suggested, since this syndrome has several causes and since each different spectral sensitivity represents a different light-absorbing substance, that wavelength limits should be established in all cases available for study.

URTICARIA SOLARE (4000-5000A). HAROLD F. BLUM, E. E. BARKSDALE and H. G. GREEN, J. Invest. Dermat. **7**:109 (April) 1946.

Spectral studies in a case of urticaria solaris in which the patient was exposed to sunlight through corning glass filters revealed that the urticaria was produced by blue and violet light with wavelengths of 4,500 to 5,000 angstrom units.

The authors feel that this type of urticaria is a distinct etiologic entity and is best described as urticaria solaris (wavelength 4,000 to 5,000 angstrom units). This eruption differs from a type of urticaria solaris produced by other wavelengths by the failure of passive transfer.

DICHLORMAPHARSEN IN THE TREATMENT OF SYPHILIS. GIRSCH D. ASTRACHAN, J. Invest. Dermat. **7**:117 (April) 1946.

The author concludes, after the administration of four thousand, three hundred and sixty-six injections, that dichlorophenarsine hydrochloride appears to be an efficacious antisyphilitic drug. Primary, secondary and tertiary lesions healed promptly

The serologic reaction of the blood improved in 64.8 per cent of the cases of late latent syphilis, in 100 per cent of the cases of early latent syphilis and 70 per cent of the cases of tertiary syphilis. The serologic reaction in cases of early syphilis changed to negative after 20.6 injections given once or twice weekly and 24.6 injections with the Eagle-Hogan method.

Toxic reactions, in general, were few, and no cases of exfoliative dermatitis, encephalitis or jaundice were encountered in this series.

Dichlorophenarsine hydrochloride was found to be less toxic but also less potent than oxophenarsine hydrochloride.

PINTA-LIKE LESIONS AMONG NATIVES OF GUAM. RALPH F. ALLEN and RAYMOND H. GOODALE, U. S. Nav. M. Bull. **46**:653 (May) 1946.

A recent survey of approximately 2,000 natives on Guam revealed 39 with hyperpigmentation and depigmentation of the skin, the lesions being limited to the extremities and the face. A high percentage yielded positive serologic reactions of the blood, although careful examination and questioning failed to reveal any evidence of yaws or syphilis.

This disease is known to the natives as "peladang" and is more prevalent in the southern half of the island, where rainfall is abundant and the relative humidity is high.

History indicates that the lesions usually appear as a small hyperpigmented area on the dorsum of the hands or feet, accompanied with mild itching of one week's duration. These areas spread slowly, and other darkened areas appear nearby and on other extremities. As the lesions increase in size the centers become depigmented, enlarge and coalesce to produce large grayish to white areas of irregular shape. No constitutional symptoms are attributed to the disease.

Observation of the fully developed condition revealed irregular-shaped areas of hyperpigmentation interspersed with depigmentation. Depigmented areas varied from grayish white to a pinkish hue, and often the alteration of pigment was symmetric in distribution.

Histopathologic examinations failed to reveal specific characteristics except for the lack of pigment in the basal cell layer from the specimens taken from depigmented areas and the abundance of pigment in the basal layer from the specimens taken from hyperpigmented areas.

Dark field examinations failed to reveal spirochetes, although the Kahn reactions of the blood were positive in all cases.

One patient who received antisyphilitic treatment on the basis of a positive reaction of the blood noted a regression of all hyperpigmented lesions. At the time of examination, only grayish areas of depigmentation were noted and the Kahn reaction of the blood was still positive.

The authors express the opinion that these cases occupy the same position among the treponematoses as pinta does in the Western Hemisphere.

CUTANEOUS DIPHTHERIA. JACK V. CHAMBERS, U. S. Nav. M. Bull. **46**:744 (May) 1946.

A case of cutaneous diphtheria is reported in which the condition originated as a blister on a lower extremity. Examination a year after onset revealed a large round ulcer, with raised rolled edges of a bluish tinge, covered with a hard leathery scab. Smears and cultures revealed Corynebacterium diphtheriae. The fermentation reaction likewise was characteristic for this organism. Results of treatment with intermuscular and local application of diphtheria antitoxin were unsuccessful at the end of seventeen days. The ulcer healed rapidly after the injection of 600,000 units of penicillin over a six day period in conjunction with topical compresses.

The author suggests that antitoxin should always be administered, in spite of its failure to produce a cure, in order to counteract possible paralysis.

OBSERVATIONS AND DATA ON PREVENTION OF POISON-OAK DERMATITIS. GEORGE G. NOVACOVICH, U. S. Nav. M. Bull. **46**:811 (June) 1946.

Poison oak dermatitis constituted one of the major causes for time lost from training at Preflight School, St. Mary's College, California. Consequently, studies were made to determine the best methods for hyposensitization and topical protection.

Hyposensitization to the ivy resin was best achieved by the use of large doses of antigens administered orally according to the recommendations of Shelmire.

Topical protection was best afforded by 10 per cent chlorinated lime ointment and Navy antigas protective ointment, through destruction or inactivation of the ivy resin. No protection was afforded by zinc oxide ointment, 10 per cent sodium perborate ointment or urea peroxide.

COMPARATIVE EVALUATION OF PREPARATIONS FOR THE PROPHYLAXIS AND TREATMENT OF FUNGOUS INFECTIONS OF FEET. MARION B. SULZBERGER and ABRAM KANOF, U. S. Nav. M. Bull. **46**:822 (June) 1946.

This study adds further data to a previous report on antifungous agents and provides additional information on the efficacy of calcium and zinc propionate powder, diodoquin powder, vioform powder, talcum powder, U. S. N. foot powder and thiourea powder in the prophylaxis of fungous infections of the feet.

Previous findings were confirmed that undecylenic powder was the most effective, practical and acceptable agent for prophylactic use in fungous infections of the feet. It was also superior in the maintainence of freedom from even minimal or "subclinical" evidences of infection. No significant differences in the efficacy of undecylenic powder or ointment were noted.

Experiments in which the patients kept their shoes and socks on continuously for seven days indicated that undecylenic powder was superior to diodoquin powder both prophylactically and in the treatment of mild infections.

DIAGNOSIS OF INFESTATION WITH "SARCOPTES SCABIEI" VAR. "HOMINIS." EUGENE A. HAND, U. S. Nav. M. Bull. **46**:834 (June) 1946.

The purpose of this article is to popularize a little known method for making the diagnosis of scabies, particularly in an atypical condition. The technic of the slice, scrape and smear method is described in detail, and photomicrographs of an acarus, acarus eggs, hezapod larvae, skeletal parts of an acarus, scybala and acarus burrows are presented as an aid in identification. The life cycle of Sarcoptes scabiei var. hominis is presented.

TREATMENT OF INFECTED SEBACEOUS CYSTS. JACK FISHMAN, U. S. Nav. M. Bull. **46**:917 (June) 1946.

A new method is described for the treatment of infected and noninfected sebaceous cysts. The technic consists in making a stab wound into the cyst, evacuating the contents and placing a small solid piece of silver nitrate into the cavity. In about twenty-four hours the wall of the cyst becomes discolored, and it is removed from the surrounding tissue by a hand forceps. The cavity is allowed to heal by granulation. No recurrences or ill effects were noted in 512 cases observed over a period of one year.

RODIN, South Bend, Ind.

DERMATOMYOSITIS AND MALIGNANT TUMOR. A. DOSTROVSKY and F. SAGHER, Brit. J. Dermat. **58**:52 (March-April) 1946.

The authors report 2 cases of dermatomyositis associated with malignant new growth. The patient in the first case was a woman aged 33 in whom a tumor of the left breast developed. This was followed, six months later, by edema, telangiectases and atrophy of the skin which, at the start, offered the aspect of acute lupus erythematosus, accompanied with pain in the joints and muscles. After the tumor had metastasized, poikilodermal features became more distinct, with atrophy of the musculature. The patient died. A striking feature was the restriction of the dermatomuscular symptoms as well as the tumors to the upper part of the body.

The second patient was a woman aged 65 in whom the entire skin, particularly on the upper part of the body, showed pigmentation, swelling, atrophy and telangiectases. There was, in addition, swelling of the muscles, paresis, dysphagia and tenderness on pressure. Gynecologic examination was made, and there was found to be a tumor of the right ovary, probably malignant. Since active treatment was

out of the question because of the poor condition of the patient, she was discharged and could not be followed further. She died two months later, and no postmortem examination was done.

The authors conclude that there is a relationship between dermatomyositis and malignant tumors. The appearance of the dermatomuscular symptoms shortly after the development of the tumor and, moreover, their intensification on metastasizing of the tumor, thereafter persisting until the patient succumbed in a state of carcinomatous prostration, would uphold their views.

SCABIES NORVEGICA IN A NATIVE OF EAST AFRICA. F. PIERS and G. L. TIMMS, Brit. J. Dermat. **58**:61 (March-April) 1946.

The occurrence of Norwegian scabies in a native of East Africa seems to be sufficiently uncommon to justify a report.

The patient, a girl of 15 years, was one of those persons "among whom washing is indulged in with the utmost caution." The patient did not complain of itching. A widespread eruption was present, consisting of round, elevated papules, measuring from the size of a pea up to a diameter of more than 2 inches (5 cm.). The areas chiefly affected were the trunk, umbilicus, lower part of the back, lateral aspects of the abdomen and thighs, buttocks, both elbows, knuckles of both hands and proximal parts of the fingers.

Histologically, in the epidermis were sections of Sarcoptes of both sexes and in all stages of development, including eggs.

BLUEFARB, Chicago.

RADIUM TREATMENT OF CARCINOMA OF THE LIP. A. A. CHARTERIS, Brit. M. J. **1**:719 (May 11) 1946.

This report covers 246 patients with cancer of the lip treated at the National Radium Center, Western Infirmary, Glasgow, Scotland, from 1928 to 1944 inclusive. The primary lesion was found on the lower lip in all except 8, in whom it was on the upper lip. With 8 exceptions the patients were men, and in only 75 instances was there sufficient doubt about the diagnosis to require microscopic confirmation. Of the patients, 208 had no obvious involvement of glands at the time of primary treatment, and, although the neck was not dealt with, in only 19, or about 9 per cent, did cervical metastases develop at a later date. The policy therefore has been to treat the primary lesion only, the follow-up examinations being relied on to detect any evidence of glandular involvement. Both implantation of radium and double radium molds were utilized in treatment, the dose delivered being from 5,000 to 6,000 r. By careful measurement of the needle pattern and placing of the plane in the center of the thickness of the lip, undesirable effects can be almost completely eliminated. When the conditions were not complicated by glandular invasion, 165, or 94 per cent, out of a total of 175 patients were rendered free from disease. When involvement of the glands was present to begin with or developed at a later date, the picture was decidedly different, in that only 25, or 48 per cent, out of 53 patients were cured. Failure of cure represented death of the patient from cancer usually about a year from treatment. In all patients treated, with or without involvement of the glands and including those rejected as untreatable and those operated on satisfactorily, the rate of cure was 73 per cent. Tabular results show that implantation methods are superior to molds.

VARICELLA HERPETIFORMIS. P. H. PETERSON and S. A. B. BLACK, Brit. M. J. **1**:762 (May 18) 1946.

The authors describe 2 cases of chickenpox which followed exposure to patients with herpes zoster on an isolated island where conditions made it unlikely that any undetected cases of chickenpox could have existed. They questioned the advisability of isolating patients with herpes zoster.

SHAW, Chattanooga, Tenn.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILOLOGY

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Oct. 2, 1945

Granuloma Inguinale. Presented by Dr. Frank C. Combes.

M. K., a Negro woman aged 55, with a past history of no significance, was admitted to the dermatologic service of Bellevue Hospital with an eruption of the groin and genital regions of five weeks' duration.

There were quarter to silver dollar size, sharply demarcated, granulating areas in the right and left inguinal regions and on the base of the major labia of the vulva, accompanied with mild edema of the vulva. The borders of the lesions were grayish white.

Laboratory Studies: A smear was positive for Donovan bodies. The Wassermann reaction of the blood was negative. Frei and Ducrey tests gave negative reactions. The urine was normal. The red blood cell count was 3,420,000; the hemoglobin content, 8.0 Gm. per hundred cubic centimeters, and the white blood cell count 13,900, with 55 per cent polymorphonuclear leukocytes, 32 per cent lymphocytes, 9 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils.

Biopsy revealed a structure compatible with granuloma inguinale.

Treatment has consisted of fuadin, 5 cc., administered intramuscularly three times weekly. Six injections have been given to date.

Frambesiform Tertiary Syphilis. Presented by Dr. Frank C. Combes.

M. B., a Negro woman aged 55, was admitted to the dermatologic ward of Bellevue Hospital with a generalized eruption of one month's duration. There is no history of previous genital sores, generalized eruption or previous injections for syphilis. The patient has never left the United States, having lived in North Carolina all her life, traveling to and from New York city for the past twelve years. The only past illness was pneumonia in 1937, at which time the blood test for syphilis gave a negative reaction.

Examination reveals discrete and confluent crusted and ulcerating lesions affecting the face, scalp, back and all extremities, with relatively few lesions on the chest. Some of the lesions are sharply demarcated from the normal skin, while others blend gradually with the surrounding tissue. The floor of the lesions appears clean and granulating, with little purulent material.

Laboratory Findings: Dark field examination for spirochetes gave negative results. The Wassermann reaction of the blood was 4 plus. The urine was normal. The red blood cell count was 4,920,000; the hemoglobin content, 11 Gm. per hundred cubic centimeters, and the white blood cell count, 26,200, with 77 per cent polymorphonuclear leukocytes, 14 per cent lymphocytes and 9 per cent monocytes.

Biopsy was reported to show "acute and chronic inflammatory reaction."

Treatment has consisted in injections of penicillin, 40,000 units every three hours.

DISCUSSION

DR. HERMAN GOODMAN: The entire face and much of the body were covered with crusts overlying pustules when the patient was first admitted to the ward. The ulcers appeared after thorough scrubbing and application of ointment. Several physicians from Central and South America discussed the possibilities of frambesia (yaws) and rupial syphilis. It is the opinion of many that this patient presents a form of syphilis with adherent crusts and that a good ablution will remove most of the superficial, superimposed layers of crust.

DR. EUGENE T. BERNSTEIN: From my experience in Russia during pre-revolutionary days, this form of syphilis is one occurring more frequently in subjects of cachexia, debauchery or extreme poverty. Syphilis frambesoides (frambesoid syphilis) is a syphilid usually observed in the third year, less often in the second, and is composed of luxuriantly suppurative warty growths. When untreated it may present a generalized eruption. The course of this nodular lesion is indolent, and resolution ensues by resorption, leaving livid, pigmented maculations at the site of the nodules. This rupioid eruption, I recall, was readily amenable to orthodox antisyphilitic therapy and did not present any therapeutic difficulties.

DR. E. W. ABRAMOWITZ: This type of syphilis is not common here. While dirt may account in part for the appearance of the lesions, I do not think it accounts for it entirely. It is due to the poor resistance of the patient. As to the question of yaws, the lesions should show an abundance of spirochetes in case of that disease, whereas there would be few or none in a syphilitic lesion in the tertiary stage.

DR. HERMAN GOODMAN: Are the terms frambesiform and rupial synonymous? The characteristic frambesiform syphilid has two, three or, at most, four lesions, each with a strawberry-like protuberance beneath the removed crust. The strawberry protuberance is not unlike granulation tissue, and the causative Treponema pertenue is easily demonstrated.

DR. EUGENE F. TRAUB: Dr. Goodman has covered most of the salient points, and I agree with him in the essentials. The widespread, generalized eruption presented by the patient does not conform to frambesiform syphilis, as taught by Dr. Udo J. Wile. It is unusual in frambesiform syphilis to have more than five or six lesions, and these lesions are most commonly scattered about the face, especially about the nose and ears. The character of the individual lesion, as has been stated, is relatively soft, fungating and suggestive of a raspberry, and not at all like an oyster shell, as are those seen in this patient. The lesions presented by Combes's patient are heaped-up crusts, of varying sizes, like the layers of an oyster shell, and represent a typical rupial syphilid. This disease was not uncommon in the West and occurred most often in women, particularly in women with poor general health and nutrition. It was looked on as a malignant type of syphilis. I believe the important consideration in cases of this type is the lowered resistance and poor nourishment rather than filth, although poverty, filth and undernourishment of course go more or less hand in hand.

DR. GIRSCH D. ASTRACHAN: I think this case is one of rupioid syphilis. The disease is not a tertiary stage but belongs to the group of late secondary forms. These appear in improperly treated syphilitic patients or in those with a low resistance. I never saw a patient with lesions as extensive as this. I am surprised that the histologic picture does not show the characteristics of syphilis.

DR. PAUL GROSS: The multiplicity of lesions and the character of the eruption would favor the diagnosis of rupioid syphilis. In that case one would have to assume that the patient's disease is in the secondary stage. The presence of ulceration shows only the appropriateness of the term syphilis precox. One can find this type of eruption even in the early secondary stage and in the presence of the primary lesion. Precocious tertiarism also expresses itself in the absence of spirochetes in the lesions, even if they represent the early secondary stage. The name malignant syphilis applies as little to this condition as it does to endemic

syphilis, which is usually of the cutaneous type and is known to have much less tendency toward visceral and neural involvement.

DR. CHARLES S. MILLER: An eruption of this type may occur in the unclean, but it is not due to uncleanliness. It is due to the histologic response elicited. Syphilis is essentially a reaction of the cutis. The epidermis may become involved secondarily. In frambesiform tertiary syphilis the cutis shows the usual syphilitic reaction, but there are pronounced changes in the epidermis and the horny zone. The epidermis shows an irregular acanthosis, elongated rete pegs, intercellular edema and notable hyperkeratosis with some areas of crusting.

DR. MAURICE J. COSTELLO: I agree with the discussers who believe that the disease is tertiary syphilis. The generalization of the eruption is in favor of the diagnosis of secondary syphilis, although the destructive process, which will terminate in scar formation, is in favor of the tertiary type.

A Case for Diagnosis: Nodular Lesions of the Face? Presented by DR. JACK WOLF.

L. C., a woman aged 38, is presented from the dermatologic clinic of Mount Sinai Hospital with two nodular lesions on the right side of the face of approximately two years' duration. The lesion over the right zygoma is an approximately pea-sized, elevated, papular, glistening lesion, pale pink and of a fleshy, elastic consistency. The bed is not indurated. The lesion below is somewhat similar in appearance, but with less elevation and a rather flattened surface, as a result of attempted removal (excision for biopsy), and possibly of previous roentgen therapy, the lesion having received 700 r in divided doses. There is an approximately dime-sized induration of the tumor bed.

The patient received antisyphilitic treatment in irregular and rather haphazard fashion for six years or more. The Wassermann reaction of the blood has consistently been negative during the past few years. Oral administration of iodides did not influence the lesions.

Histologic examination was performed on three occasions, with the following reports:

1. "Fragment of skin showing granuloma with conspicuous eosinophilia."

2. "Section of skin showing striking capillary proliferation with a diffuse inflammatory reaction. The histologic picture is equivocal and could be that of granuloma or an inflamed angioendothelioma. I prefer the first alternative (granuloma) but would recommend that the patient be kept under close observation."

3. "Chronic nonsyphilitic inflammation with a conspicuous number of eosinophils and circumscribed necrosis. The histologic structure rules out sarcoid and tuberculosis, but the lesion could be a persistent papulous urticaria."

DISCUSSION

DR. MAX SCHEER: It has been impossible to make a clinical diagnosis, though it might be sarcoid; several histologic reports, however, do not bear out such a diagnosis. There are many eosinophils in the slide, and I thought the lesion might be one of those rare eosinophilic granulomas, but Dr. Otani, of the department of pathology, saw the slide again and could not make a diagnosis. It is impossible to make either a clinical or a histologic diagnosis at present.

DR. CHARLES WOLF: I should like to ask the presenter whether at any time there was a discharge from the lesions. [Answer: No.] I was thinking of the possibility of actinomycosis.

DR. CHARLES S. MILLER: I suggest the possibility of Spiegler-Fendt sarcoid. I had a patient with similar lesions, and examination revealed the pathologic changes of this sarcoid.

DR. SAMUEL M. PECK: Surely the histologic picture gives some indication of the diagnosis. The very fact that three sections were taken and that these three

sections showed such diverse histologic structures proves that the lesion is not a specific granuloma. The histologic data, even if not specific, can be used to rule out certain conditions. In looking at the lesions, one would certainly think first of sarcoid. I cannot think of any type of sarcoid, either the Boeck or the Spiegler-Fendt, that would resemble the histologic pictures seen here. If one palpates the lesions, one feels a little cord connecting them. Why cannot the diagnosis be something simple? In the lower lesion, at the periphery one finds a few large follicular openings, resembling comedos. Why may this not be a chronic infectious, cystlike lesion? When the sac is ruptured and the sebaceous material comes into contact with collagen, it forms a granuloma of a tuberculid type. I suggest the diagnosis of a beginning keloid in an infected cyst.

Syringoma. Presented by DR. MAX SCHEER.

I. K., a man aged 49, is presented from the dermatologic clinic of Mount Sinai Hospital with an extensive eruption of at least ten, and possibly twenty, years' duration. The eruption is widespread. Lesions are present on the trunk, chiefly along the anterior aspect; on the inner aspect of the upper extremities and to a lesser degree on the thighs and neck. The greatest profusion of lesions occurs along the lower part of the chest wall and along the forearms, and here they are also particularly developed. The individual lesion is approximately the size of a matchhead, smooth, discrete, fleshy and of a moderately intense red color. The less developed lesions are smaller and are more yellowish.

Biopsy was reported by Dr. Paul Klemperer to show a structure consistent with a diagnosis of syringoma. In the corium there were many cysts lined with epithelial cells.

DISCUSSION

DR. EUGENE T. BERNSTEIN: This is a classic case of syringoma occurring over the chest and extending to the extremities. The eruption is composed of fawn colored to yellow globoid nodules ranging from the size of a pinhead to that of a split pea and larger and presenting a somewhat waxy appearance. The lesions are slightly elevated. The patient has no subjective symptoms, and the general health is unimpaired. Syringoma usually occurs in women, and the establishment of the clinical diagnosis is not particularly difficult. The lesion is regarded as a new growth derived from misplaced embryonic sweat ducts or sweat glands. Weidman expressed the belief that the condition is a true adenoma of the sweat glands. Homma and Escher raised the question of the origin of syringoma in the apocrine glands (Genesis of Syringoma, ARCH. DERMAT. & SYPH. **33**:700 [April] 1936).

DR. E. W. ABRAMOWITZ: Histologic examination is the final desideratum in the diagnosis. Clinically, syringoma is frequently associated with other types of lesions, such as multiple benign cystic epithelioma of the eyelids and involvement of the axillary region. Many years ago at the Vanderbilt Clinic, Dr. John Remer presented a case of syringoma in which he obtained involution with fractional doses of roentgen rays. In my first case I had a similar result. Fourteen or sixteen fractional doses (75 r each), unfiltered, caused a remarkable involution.

DR. EUGENE T. BERNSTEIN: A distinction should be drawn between syringoma and multiple benign cystic adenoma (Jarish). Multiple benign cystic adenoma begins at the age of puberty, is frequently hereditary and is seen in several members of the same family. The lesions are conspicuous in their occurrence about the face. The origin of these growths is in the basal layer of the epidermis or similar cells of the hair follicles, and not from the sweat glands, as is the case in syringoma.

DR. OSCAR L. LEVIN: This case represents a disease which is usually more localized. The histologic structure is characteristic of syringoma, and clinically several disorders are suggested. Multiple benign cystic epithelioma tends to be more localized to the chest, face and neck. The lesions are firm and tend to show central depressions. The histologic structure is different from that of syringoma, revealing strands and masses of epithelium, with a tendency to formation of cysts

containing horny material. There may be structures suggestive of hair follicles and sebaceous glands. Syringocystadenoma is usually yellower and softer, and the pathologic picture resembles that of multiple benign cystic epithelioma, revealing also structures suggestive of tubules and coiled glands. In the present case the lesions are soft, as is usually observed in cases of syringoma, and generalized, and the diagnosis of syringoma must be accepted because of the histologic picture. Roentgen irradiation will not be of benefit in the first two lesions mentioned, but may be of value in destroying the syringoma.

DR. CHARLES S. MILLER: The diagnosis in a case of this type is usually made histologically. The term "syringoma" should be applied to a nevoid condition arising from the duct part of the sweat duct system. "Syringocystadenoma" is frequently used interchangeably with "syringoma," although it denotes a histologic picture in which there are more elements of the sweat ducts, some of which show dilatation. The term "spiroadenoma" refers to a nevoid condition arising from the coil, or secreting, portion of the sweat gland system.

DR. JACOB SKEER, Brooklyn: In 1936 I saw a similar case, that of a single white woman aged 22 (Syringocystadenoma, ARCH. DERMAT. & SYPH. **40**:268 [Aug.] 1939), with an eruption of exceptionally wide and unusual distribution of twelve years' duration. The lesions were irregular, flattened papules situated on the neck, shoulders, axillas, chest, hips and thighs. The histologic report by the late Dr. D. L. Satenstein was syringocystadenoma. The patient had tuberculosis and was in a sanatorium. She received two courses of roentgen therapy, in doses of 150 r each, at intervals of two weeks, for a total of six treatments, after which the lesions appeared flatter. New lesions continued to appear. Three years later the lesions were still present.

DR. MAURICE J. COSTELLO: I should like to suggest to the presenter that if roentgen therapy is used here only one side of the body be treated. Dr. Fox had a patient with a similar, but less extensive, eruption to whom fractional doses of roentgen rays were administered, causing involution of lesions on one side of the body.

METROPOLITAN DERMATOLOGICAL SOCIETY

Royal M. Montgomery, M.D., *President*

James Lowry Miller, M.D., *Secretary*

New York, Oct. 15, 1945

Rosacea. Presented by DR. JOSEPH C. AMERSBACH.

A. P., aged 48, shows hypertrophy of the nose associated with redness, telangiectasia and papulopustules. He has received roentgen therapy, applications of solid carbon dioxide, sulfur pastes and lotions, and dilute hydrochloric acid, with only moderate improvement.

The patient is presented for suggestions as to therapy.

DISCUSSION

DR. LESLIE P. BARKER: This patient had definite rosacea of the tip of the nose. The cause is difficult to determine. I think the best result can be obtained with scarification, but it would require repeated treatments. Peeling doses of cold quartz-mercury vapor radiation, along with scarification, may also help.

DR. MAURICE J. COSTELLO: I do not think that this patient has rosacea. I think the eruption is a dilatation of the blood vessels of the bulbous portion of the nose, secondary probably to trauma. I have seen this clinical picture follow infections of the nose, such as carbuncles and furuncles, and, especially, operations on the nose and sinuses. There is nothing, in my experience, that will help him, short of surgical diathermy, in which one runs the risk of scar formation.

DR. THOMAS N. GRAHAM: I am inclined to agree with Dr. Costello. I have cases similar to this at the New York Eye and Ear Infirmary in which there has been a nasal operation. This patient does not show the characteristic features of rosacea. The disturbance is probably a circulatory deficiency, which will not respond to any form of therapy.

DR. JOSEPH C. AMERSBACH: I have had many cases of this type, and often I am in doubt as to whether they are true cases of rosacea.

Epidermodysplasia Verruciformis. Presented by DR. ROYAL M. MONTGOMERY.

C. R., a white woman aged 28, has had the present disease for twenty years. She was first seen April 13, 1945.

There are many flat, shiny-topped papules on the fingers and the dorsa of the hands. Many are grouped on the fingers. Some are flesh colored; others are red. There are similar flat, verrucous lesions on the dorsum of the right foot and the ankle.

Roentgen therapy and six intramuscular injections of bismuth salicylate have failed to produce any improvement.

The biopsy report on a lesion (Dr. Charles F. Sims) follows: "The epidermis presents an irregular surface, covered in part with a mild, loosely laminated horny layer. At two points in the section there is moderate acanthosis. In these areas the granular layer is absent for the most part. The rete presents numerous vacuolated cells, producing a basket-weave effect. The corium reveals no noteworthy changes."

The diagnosis is epidermodysplasia verruciformis.

DISCUSSION

DR. MAURICE J. COSTELLO: I agree with the diagnosis of epidermodysplasia verruciformis, although the eruption is not so extensive as in some cases that I have observed. I believe that these lesions can be successfully treated with the electric cautery (fractional method).

DR. THOMAS N. GRAHAM: I agree with the diagnosis. It has been proved by biopsy.

DR. JOSEPH C. AMERSBACH: I understand that no new lesions have appeared since the onset. I should therefore suggest excision with the scalpel, rather than treatment by desiccation.

DR. LESLIE P. BARKER: I agree with the diagnosis of epidermodysplasia verruciformis, and I think these lesions should be destroyed by electric desiccation, as they often develop into basal cell epitheliomas. I had a case of extensive involvement a few years ago in which superficial basal cell epitheliomas developed in the lesions. Many lesions resembled atrophic lichen planus, while others resembled the papular type of lichen planus.

DR. ROYAL M. MONTGOMERY: I believe all lesions should be destroyed. If not destroyed, some will later show epitheliomatous changes. The patient does not approve of having them destroyed. She realizes it will cause scarring.

A Case for Diagnosis (Dermatitis Venenata? Erythroplasia?). Presented by DR. LESLIE P. BARKER.

E. K., aged 43, was first seen eight months ago, at which time he gave a history of having had a slightly itchy, nonpainful eruption on the glans penis of two months' duration. The lesion practically cleared twice but soon recurred. He denied taking any drugs, and neither he nor his wife used contraceptives. His general health was good. He denied having had any venereal disease.

Examination reveals a patchy, circumscribed lesion involving the larger part of the distal half of the glans penis and extending around the meatus. The lesion is bright red and granular, and there is a serous discharge with crusting.

Treatment has consisted in use of fractional doses of roentgen rays, with a total dose of 600 r, and soothing ointments, such as starch in cold cream and plain white petrolatum. The patient has abstained from all friction or irritation. The Wassermann reaction of the blood was negative.

The biopsy report follows: "Sections of the lesion stated to have been removed from the penis disclosed edematous stratified squamous epithelium, which had undergone hyperplasia. A detached scale of parakeratosis was present. Leukocytes had infiltrated both the epithelium and the underlying stroma. The latter was the site of a profound chronic inflammatory reaction, with many plasmacytes and a few eosinophils. There were no pathognomonic changes."

DISCUSSION

DR. MAURICE J. COSTELLO: This lesion impressed me as one of erythroplasia, especially since it began on the glans penis, increased gradually and slowly and never receded. The lesion must have a fair amount of exudation because it is covered with a crust. I think the lesion is preepitheliomatous and should be destroyed adequately. I have destroyed several of them with electric desiccation, sometimes repeating the treatment a second or a third time before the lesion finally disappeared.

DR. THOMAS N. GRAHAM: I agree with Dr. Costello.

DR. ROYAL M. MONTGOMERY: A few years ago Dr. Lapowski showed several cases of this type at a meeting of the Section of Dermatology and Syphilology, the New York Academy of Medicine. He used a paste of resorcinol and an aluminum tube as protection and had remarkable results. Since fractional doses of roentgen rays and soothing ointments have been used without results, destruction is now in order.

DR. JOSEPH C. AMERSBACH: I believe this is the type of case in which a proper diagnosis cannot be made by microscopic study alone.

DR. RICHARD J. KELLY: I think this case falls in with 50 or 60 cases described by Madden before the Section on Dermatology and Syphilology at the annual session of the American Medical Association at Atlantic City, N. J., in 1933 (Generalized Angiomatosis, J. A. M. A. **102**:442 [Feb. 10] 1934). He had studied carefully for a period of four or five years cases like this in which the lesions were resistant to local therapy but did respond to roentgen radiation and radium. He felt that the latter was the proper method of treatment. I have seen only 2 or 3 patients with this disease, and all have responded properly to roentgen or radium therapy. I agree with the diagnosis of erythroplasia.

DR. LESLIE P. BARKER: I think this is a case of erythroplasia, although during the first few weeks that I treated this patient the eruption reacted more like dermatitis venenata. It cleared almost completely with soothing applications and then reappeared suddenly after the patient had applied an irritating ointment.

I hesitated to destroy the area with electrodesiccation because it involved the meatus. I shall use superficial radium therapy and report later on the result.

Erythema Perstans. Presented by DR. ROYAL M. MONTGOMERY.

J. S., a Cuban aged 39, has had the present eruption for four years. He was first seen at the New York Skin and Cancer Unit on July 31, 1945.

In the groins, axillas and about the upper portions of the thighs he has erythematous, semicircular patches which have slightly raised, nonvesicular borders. The centers of the patches are slightly pigmented and scaly. They tend to heal spontaneously, with a new patch appearing nearby. The patient has had a duodenal ulcer.

Examination for tinea gave negative results. The Wassermann and Kahn reactions of the blood were negative.

Ten thousand units of penicillin was given on Sept. 18, 1945 for a streptococcic infection. This caused a slight flare-up of the eruption.

DISCUSSION

DR. THOMAS N. GRAHAM: I think this is a case of erythema annulare centrifugum, because the patient gives a history of the annular lesions starting with a single papule which spreads peripherally to form a circle of papules. The lesions also show a crater-like sloping of the inner borders. This feature was described by Darier. Erythema perstans usually presents only one or two lesions. Both diseases are probably related to erythema multiforme. Dr. Throne and I treated 5 patients with a bismuth preparation, 2 of whom apparently responded, but they had remissions (Graham, T. N., and Throne, B.: Erythema Annulare Centrifugum, ARCH. DERMAT. & SYPH. **22**:777 [Nov.] 1930). We were therefore not certain whether or not bismuth therapy was effective.

DR. RICHARD J. KELLY: I agree with Dr. Graham. I think this case fits in with his description.

DR. MAURICE J. COSTELLO: I agree with everything Dr. Graham has said. I have heard that intramuscular injections of bismuth subsalicylate are of value in this dermatosis. I never had the success that others claim with this form of therapy. I should like to hear discussion on that point.

DR. ROYAL M. MONTGOMERY: The term erythema perstans covers a wide variety of lesions. My impression of erythema annulare centrifugum is that concentric, multichromatic, halo-like lesions are present In this case one sees one lesion only with a semicircular border. It was suggested by an internist, who saw this patient with me, that saline catharsis, together with succinylsulfathiazole, be prescribed. The patient has received this therapy for a week. He has shown improvement. The same therapy will be continued. He was taking 2 Gm. of the drug every three hours with an alkali. If this does not help, a bismuth preparation will be given. (A week later the patient showed 80 per cent improvement.)

Purpura Annularis Telangiectodes. Presented by DR. ROYAL M. MONTGOMERY.

J. T., a nurse aged 18, has had the present eruption for one month. For the past year and a half there has been a small eczematous patch on the dorsum of the left foot. The newer lesions spread from this patch about one month ago.

At present there is a small dry, eczematous patch on the dorsum of the left foot. Small red papules are present in this area. There are many scattered pinpoint, red or telangiectatic papules near this eczematous area. These are also found on the dorsa of the toes of both feet and about the heels.

Examination of the blood showed 97 per cent hemoglobin (14.1 Gm. per hundred cubic centimeters), 4,500,000 erythrocytes and 130,000 platelets.

The patient has been taking 300 mg. of ascorbic acid daily. There has been no improvement.

DISCUSSION

DR. JOSEPH C. AMERSBACH: I agree with the diagnosis, and I myself have had several cases of this type in the past few years. It is my belief that a further search should be made for foci of infection. However, many times no foci of infection can be found. When no such foci are present, I am generally content to use roentgen rays and lotions, which usually control the associated pruritus and clear up the eruption temporarily.

DR. RICHARD J. KELLY: I think this patient has a vasomotor disturbance. I believe a test of vascular function should be made before any other determinations. She should have a thorough examination, including hepatic function tests. If there is any way of testing her for sensitivity to histamine or histaminase, it should be done.

DR. MAURICE J. COSTELLO: I do not think any one can make that diagnosis clinically. It may be suspected. I presented patients before several of the societies whom I had observed for years. One was a young woman with an eruption which resembled this in the beginning and later showed areas of atrophy, hyperpigmentation and depigmentation. That girl went from one dermatologist to another and

from clinic to clinic. I finally gave her gold sodium thiosulfate. After she had received twelve injections the eruption disappeared. Examination three years later showed that she had had no recurrence except for a little breaking down around the ankle, which had occurred only a few days previously.

DR. THOMAS N. GRAHAM: The lesion on the left ankle could well be hypostatic eczema. The other lesions are purpuric and could be on a hypostatic basis. The patient stands a great deal, resulting in dilatation of the veins. I cannot see anything at present on which one could base a diagnosis of purpura annularis telangiectodes. There is no atrophy, as Dr. Costello pointed out, and no annular areas. I favor a diagnosis of hypostasis, producing eczema and purpura.

DR. J. LOWRY MILLER: I agree with the statements of the last speaker. I have successfully used blistering doses of ultraviolet radiation in 2 cases. There is no danger in this therapy, and it may be successful.

DR. ROYAL M. MONTGOMERY: As for giving blistering doses of ultraviolet radiation therapeutically, it would be best to check on the condition of her vascular system first. I do not believe this therapy would help. This case suggests an early purpura annularis telangiectodes. Perhaps I should have presented the case with the present diagnosis and a question mark.

Dermatophytosis of the Hands and Feet: Tinea Corporis (Glabrosa).
Presented by DR. ROYAL M. MONTGOMERY.

J. G., a white man aged 24, who was first seen on Oct. 5, 1945, has had the present eruption for two years and three months. He was with the Navy in the Solomon Islands when the eruption first started.

On the dorsum of the right hand there is a dull red, scaly dermatitis with some formation of papules. On the index and ring fingers of this hand there is a white linear streak across the center of the nail plates. This eruption extends on to the wrist. On the palm the skin is thickened, dull red and slightly scaly. Several dried pustules are present. These also extend on to the wrist. The left hand is normal.

There is a red, scaly patch on the outer side of the right ankle just behind the malleolus. On the dorsa of both feet there are scaling, erythematous patches with some extension toward the toes. On the soles and extending on to the instep there are scales and erythematous macules. On the anterior surface of the right knee there is also a scaly, red patch. There are similar areas in the groins and on the buttocks.

Examination of material from the dorsum of the hand and the foot for tinea gave positive results. Cultures have not had time to grow.

DISCUSSION

DR. R. C. CARLISLE (by invitation): I have seen many cases similar to this. It is often necessary to try many kinds of therapy until a suitable one is hit on. Recently, I saw a case of the infection contracted in Guadalcanal which had not responded very well to any type of treatment. The lesions are often made worse with ultraviolet radiation therapy; in fact, it is easy to make them worse.

DR. RICHARD J. KELLY: Dr. Montgomery knows more about how to kill the fungus than I do; on the other hand, I am inclined to agree with Dr. Carlisle that trial and error is usually necessary. I would suggest that the parts be elevated and kept dry until more drastic measures are decided on. I should use roentgen radiation and powder at the present time. Climatic conditions were responsible for the severity of the lesions in many instances. Even the natives had similar conditions.

DR. MAURICE J. COSTELLO: It is my opinion that the patient has an infection with Trichophyton purpureum. No one sees many cases of this disease in private practice; as is well known, the infection is resistant to therapy. I have had a degree of success with anthralin ointment (1 or 2 per cent anthralin in a petrolatum base) and chrysarobin, 10 to 20 per cent.

DR. THOMAS N. GRAHAM: I agree with the diagnosis. Vioform, 10 to 20 per cent in petrolatum, might also be tried. This ointment is effective in some cases of dermatophytosis in which other measures produce no improvement.

DR. J. LOWRY MILLER: I have used both undecylenic acid and propionic acid in these cases, without any benefit.

DR. ROYAL M. MONTGOMERY: I agree that these cases always present a problem. Roentgen irradiation is contraindicated because it results in no therapeutic response. I think the lesions should be treated with strong fungicidal remedies. This will be a good case in which to try it. This patient presents another problem in that he is training to be a chiropodist. If he does not clear his hand, he may infect his patients, and incidentally increase his business tremendously. He was told by five Navy dermatologists that his present disease is incurable. Perhaps I should agree with them.

A Case for Diagnosis (Vascularitis of Unknown Origin?). Presented by DR. J. LOWRY MILLER.

R. S., a woman aged 21, was seen by the presenter at the Presbyterian Hospital on Sept. 8, 1945. At that time she complained of a macular rash on the forearms and the dorsal and palmar surfaces of the hands of six months' duration. During the six months the rash had been present a splenectomy was performed for idiopathic thrombopenic purpura. The symptoms prior to operation had been bleeding gums, ecchymoses of the body, epistaxis and tarry stools. The platelet count prior to operation had fallen to 4,000, and by the tenth postoperative day it was 351,000. The patient had postoperative elevations of temperature to as high as 104 F., for which penicillin, sulfadiazine and blood transfusions were given. Penicillin and sulfadiazine had no effect on the temperature, which gradually cleared as a pleural effusion on the left side absorbed. The patient did not complain of symptoms connected with the rash but did have generalized weakness. A diagnosis of Still's disease (multiple rheumatoid arthritis) had been made on his admission to Presbyterian Hospital in 1938. Similar cutaneous lesions were described as present at that time.

On both surfaces of the hands and, to a less extent, on both surfaces of the forearms, there are red, split-pea-sized macules which fade on pressure. There is no scaling.

The electrocardiogram was normal. A blood count showed 11 Gm. of hemoglobin per hundred cubic centimeters, 4,000,000 red blood cells and 10,000 white blood cells, with a normal differential count. The sedimentation rate varied from 90 mm. in one hour to normal. The blood platelet count at the time of her discharge from the hospital was 351,000. Roentgenologic examination of the chest revealed nothing abnormal. The urine was normal except for a 2 plus reaction for albumin.

DISCUSSION

DR. RICHARD J. KELLY: This patient has a muscular dystrophy. I think that she also has a disturbance of the sympathetic nervous system. Her palms and feet perspire constantly. She has lost 20 pounds (9.1 Kg.) in weight. Her appetite is normal to all appearances, but she does not gain any weight. I agree with Dr. Miller when he says that the lesions on the shoulders might be evanescent. They have appeared and have gone away before. I think the diagnosis is some type of progressive muscular dystrophy, which I shall have to leave for the other members to decide on.

DR. MAURICE J. COSTELLO: I agree with the diagnosis of Still's disease. This girl has bilateral synarthrosis with large joints, which show no changes on roentgenographic examination, in addition to anorexia, loss of weight, a cachectic appearance and retardation of growth of the skeletal system. I believe that the eruption she presents is associated with the disease. The prognosis is unfavorable.

DR. THOMAS N. GRAHAM: I do not think that this case is one of dermatomyositis with acute lupus erythematosus. The lesions on the dorsa of the hands

are not the type found in lupus erythematosus. I cannot suggest a diagnosis in this case.

DR. JOSEPH C. AMERSBACH: I am not acquainted with the diagnosis in this type of case. Since the lesions fade, I believe the eruption to be a toxic manifestation associated with the general condition of the patient.

DR. J. LOWRY MILLER: I presented this case for suggestions as to the significance of the macular lesions. On the one hand, they may represent the early stages of one of the so-called vascular diseases; on the other hand, they may be the residua of gradually resolving Still's disease. The fact that they were described when the patient had Still's disease, at the time she was first observed, is in favor of the latter view.

Granuloma Annulare. Presented by DR. J. LOWRY MILLER.

C. H., a girl aged 7 years, was seen at the Vanderbilt Clinic with the complaint of red lesions on the right thigh and right ankle, which had been present for one year. The patient had noted no symptoms except the gradual enlargement of the lesions. She denied having taken any medicament by mouth.

On each of the aforementioned locations there is present a circular lesion the size of a silver dollar. The border is made up of erythematous, closely grouped nodules, and the center is clear. In places the ring is undergoing involution and has a crescentic configuration.

DISCUSSION

DR. ROYAL M. MONTGOMERY: I agree with the diagnosis. The border is less erythematous but more indurated than that in the case I presented. The 2 cases belong in the same category.

DR. JOSEPH C. AMERSBACH: I agree with the diagnosis of granuloma annulare.

DR. LESLIE P. BARKER: The lesion consists of split-pea-sized, firm, grayish nodules arranged in a circinate fashion. Clinically it is typical of granuloma annulare.

DR. RICHARD J. KELLY: I agree with the diagnosis. May I ask the presenter whether roentgenograms were taken of the chest, the fingers and the extremities?

DR. J. LOWRY MILLER: No, they have not been taken yet.

DR. MAURICE J. COSTELLO: I think I agree with the diagnosis of the lesion on the ankle. I was under the impression that in granuloma annulare the border is continuous. In both lesions the border is absent in one segment, which made me feel that the child has erythema annulare centrifugum. A biopsy should be performed to clarify the point.

DR. J. LOWRY MILLER: At the time the patient was first seen erythema annulare centrifugum was considered as a possible diagnosis. I believe this is a case of granuloma annulare because the lesion is present in a child and because of the hard border. I have seen, and I think there have been described, cases in which part of the border has disappeared.

NOTE.—Histologic examination was reported to reveal granuloma annulare.

A Case for Diagnosis (Psoriasis? Onychomycosis?). Presented by DR. J. LOWRY MILLER.

R. B., a woman aged 49, was first seen by the presenter one week ago, complaining of a yellowish discoloration and crumbling of the nail of the fourth finger of the left hand. She had noticed this change for the past three months. She had never had any cutaneous lesions or symptoms of arthritis.

The entire nail of the left fourth finger is yellowish, thickened and distorted. The bases of all the other finger nails are covered with stippling. There are no changes along the edges of the nails. Between the third, fourth and fifth toes there is whitish maceration. The toe nails are normal. The scalp and elbows are clear.

Fungus was revealed on microscopic examination of material from the toes but not from the finger nails.

DISCUSSION

DR. JOSEPH C. AMERSBACH: I suggest that the diagnosis be withheld until a report of the culture is obtained.

DR. LESLIE P. BARKER: I think the condition of the nails is due to a fungous infection rather than to psoriasis. There are no lesions elsewhere on the body, and the nail shows ridging, discoloration and thickening, with only pseudopitting. The pitting of psoriasis is usually characteristic, although not present in all cases. Cultures should be made for fungi.

DR. R. C. CARLISLE (by invitation): I favor the diagnosis of fungous infection.

DR. RICHARD J. KELLY: I agree with Dr. Carlisle that it is a fungous infection.

DR. MAURICE J. COSTELLO: The evidence is in favor of psoriasis; for fungous infection to involve all the finger nails takes years; then, again, usually one or two nails would be free of infection. All the nails are involved in this case. I think the pitting is suggestive of psoriasis.

DR. THOMAS N. GRAHAM: I agree with Dr. Costello. There does not seem to be any undermining of the margin of the nail, which one usually sees with fungous infections of the nails. I thought I saw definite pitting, which of course is a feature of psoriasis of the nails.

DR. ROYAL M. MONTGOMERY: One always hesitates to make a diagnosis of psoriasis of the nails without other cutaneous lesions. Dr. Costello mentioned that pitting developed in all the nails at the same time. This is against the diagnosis of onychomycosis. Clinically it does not impress me as a fungous infection. Several examinations for tinea should be done to rule out that possibility.

DR. J. LOWRY MILLER: Even if fungi are found in culture of material from the nails in this case, I doubt whether fungous infection is the underlying cause. The pitting of all the nails, the absence of paronychia and the sudden onset all favor a diagnosis of psoriasis. However, that diagnosis cannot be made until more positive proof is present.

A Case for Diagnosis (Superficial Epithelioma? Bowen's Disease? Roentgen Ray Dermatitis? Neurodermatitis?). Presented by DR. J. LOWRY MILLER.

A. I., a woman aged 62, was first seen at the Vanderbilt Clinic Oct. 8, 1945, complaining of lesions on the left side of the chest, the left axilla, the right shoulder and the extensor surfaces of both elbows. She stated that the lesion on the left side of the chest had been present for five years, the lesion in the left axilla for three months, the lesion on the right shoulder for many years and the lesions on the elbows for several years.

She had had a mastectomy of the left breast for cancer twenty-seven years ago and a similar operation for cancer of the right breast thirteen years ago. Metastasis to the nodes of the right axilla had occurred before the second mastectomy, and she was given massive radiation therapy for these nodes. For the past five years she had noticed a gradually enlarging lesion of the left side of the chest, and for the past three months, a similar lesion in the left axilla. Itching lesions have been present on both elbows for several years.

On the left side of the chest there is an erythematous lesion the size of a 50 cent piece studded with pinhead-sized, hyperkeratotic areas. In the left axilla there is a dime-sized, slightly elevated circular lesion with no ulceration. On the left side of the chest, the right axilla and the right shoulder there are white atrophic areas in which there are many telangiectases. On the elbows there are red, lichenified patches.

DISCUSSION

DR. LESLIE P. BARKER: The lesions have the appearance either of Bowen's disease or of superficial basal cell epithelioma developing on a dermatitis due to roentgen rays. They should be destroyed by electrodesiccation.

DR. R. C. CARLISLE (by invitation): The largest lesion looked like a superficial basal cell epithelioma. It could be a lesion of Bowen's disease.

DR. RICHARD J. KELLY: I think the lesion might be classified as Bowen's disease clinically, but biopsy should be performed. There are nodules under her skin. I remember a case Dr. Amersbach presented before this society two or three years ago in which there was multiple basal cell epithelioma. I should be interested in having him discuss this case. I found other nodules that might or might not be described as pathognomonic.

DR. MAURICE J. COSTELLO: It is impossible to make a definite diagnosis of epithelioma at this time, but I should suspect the presence of such a neoplasm, since one of these lesions occurred on devitalized skin. I think it should be treated as prickle cell epithelioma.

DR. THOMAS N. GRAHAM: My impression is that the eruption in the left axilla may be seborrheic dermatitis. The patient has seborrhea of the scalp. A biopsy of the other lesions should be made before deciding on the treatment. They may well be epitheliomas.

DR. ROYAL M. MONTGOMERY: Without a biopsy, I favor the diagnosis of superficial basal cell epithelioma rather than Bowen's disease. In the cases of Bowen's disease I have seen there was not as much infiltration as in cases of superficial basal cell epithelioma. In the former disease there is a smoother lesion. However, I think a biopsy must be made to make the exact diagnosis.

DR. JOSEPH C. AMERSBACH: The lesion impressed me as one of Bowen's disease; if not this, it may be either basal or prickle cell epithelioma. Regardless of the true diagnosis, I think that the adequate treatment is electrosurgical. The lesion in the axilla is probably associated with other areas of dermatitis on the arms and elbows.

DR. J. LOWRY MILLER: This case is one of unusual interest because of the history of cancer of one breast twenty-seven years ago and cancer of the other breast thirteen years ago. The diagnosis in both instances was established by biopsy. In the second instance metastasis to the regional axillary node had occurred. The treatment was radical mastectomy followed by roentgen irradiation. A superficial type of epithelioma arising in an area of dermatitis due to roentgen irradiation presents to my mind a difficulty in classification.

Erythema Multiforme Bullosum and Dermatitis Medicamentosa [Sulfonamide Compounds]. Presented by DR. MAURICE J. COSTELLO.

K. R., a Negro aged 52, has an eruption which has occurred in three more or less separate attacks over the last two months. At present the third exacerbation is subsiding. The patient began to have vesicles on the tongue about two months before admission (Aug. 1, 1945). Two or three days previously he had had a sore throat and mild nasopharyngitis, which he believes was a "cold." He was treated (for the lesions on the tongue) by a local physician, who gave him tablets and a mouth wash. In about three weeks the lesions cleared up. Two weeks after the first lesions had subsided, the lesions on the tongue reappeared, and at the same time a small, tack-head-sized vesicle appeared on the dorsum of the left wrist. This blister ruptured, and the subsequent denuded area spread peripherally to become the size of a nickel. The denudation remained fairly superficial, and subjective symptoms were slight. He visted another local physician, and, after local and oral therapy for about a week, the lesions again regressed. Two weeks later vesicles reappeared on the tongue and in the mouth; the lesion on the wrist flared up again and was the site of a papulovesicular eruption. New vesicular lesions appeared on the arms, scrotum, penis and legs and, lastly, on the face and forehead.

These new lesions became denuded and especially raw on the scrotum, where pruritus was severest.

Two months before the initial outbreak he had had sexual intercourse, but not since. He has had several colds during the winter and one a short time before the initial outbreak of the present eruption. The temperature has been normal. Urinalysis and examination of the blood gave normal results. On Oct. 3, 1945 the Wassermann and Kahn reactions of the blood were negative. Dark field examination for Treponema pallidum on Oct. 2, 1945 gave negative results.

DISCUSSION

DR. THOMAS N. GRAHAM: I agree that the most likely diagnosis is erythema multiforme bullosum, probably due to medication with sulfonamide compounds. Bullous eruptions are not uncommon after ingestion of these drugs.

DR. ROYAL M. MONTGOMERY: An interesting fact about cases of sulfonamide dermatitis is that a flare-up may occur when one thinks the patient is well on the road to recovery.

DR. LESLIE P. BARKER: The eruption was typical of erythema multiforme bullosum. The interesting feature, however, was the appearance of the eruption so long after use of the drug had been stopped. It is common for sulfonamide eruptions to appear from nine to fourteen days after the drug is discontinued, but in this instance it was considerably longer.

DR. J. LOWRY MILLER: I have seen a similar case in which there was this relatively long period after taking the drug before the onset of symptoms.

DR. R. C. CARLISLE (by invitation): The picture in this case is compatible with the present conception of drug sensitization. A period of incubation is required before the patient is sufficiently sensitized to whatever residual amount of the drug remains in the body, Also, this sensitization, once occurring, does not necessarily remain but may disappear and reappear, thus giving rise to recurring eruptions without further ingestion of the offending drug.

DR. MAURICE J. COSTELLO: In my experience, bullous eruptions following sulfonamide drugs are not frequent. The interesting feature in this case is the loss of so much fluid and blood from the mucous membrane.

Erythema Multiforme Bullosum (Due to Sulfonamide Medication). Presented by DR. MAURICE J. COSTELLO.

J. W., two weeks previous to admission, was treated by a local physician with sulfathiazole for "lung trouble." He took the drug for fourteen days (dosage unknown). Two days before admission (October 1) his lips became swollen, edematous and denuded and began to bleed. A day later there were a slight bloody discharge from the penis and vesicles "all over the body."

On his admission, examination showed edematous, bleeding lips and buccal mucous membranes and a generalized eruption of flaccid, irregular bullae. The patient had had a sore throat one week before the outbreak of the present eruption.

The Wassermann reaction of the blood was negative; the blood count and the urine were normal. The temperature was normal. The patient felt quite ill when admitted and for two to three days afterward, but at present has few general complaints.

DISCUSSION

DR. LESLIE P. BARKER: The lesions have the appearance of a fixed eruption. I should investigate the possibility of the patient's having taken any phenolphthalein, either as a cathartic or in foods or candies; it is often used as a coloring in confectionery.

DR. THOMAS N. GRAHAM: I agree with the diagnosis of erythema multiforme bullosum. I do not think the eruption was apparent enough tonight to justify that diagnosis, but from the description I should accept it.

DR. ROYAL M. MONTGOMERY: This case impresses me as one of an eruption caused by a drug. The lesion on his arm makes one strongly suspicious of phenolphthalein because of the color. He may have ingested it in candy or cake. Phenolphthalein may cause a vesicular or an eczematous eruption.

DR. MAURICE J. COSTELLO: I agree with the diagnosis that this is a fixed eruption, probably due to a drug. He had an exacerbation of previous lesions after ingestion of the drug, such as the formation of an erythematous halo, the center of the lesions becoming bullous.

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Oct. 19, 1945

Granuloma Annulare. Presented by DR. MEYER L. NIEDELMAN.

M. D., a white man aged 50, of good general appearance, three years ago noted a lesion on the inner proximal area of the right index finger. It was treated with roentgen rays and now appears as a circumscribed area of erythema with atrophy in the center. There is a suggestion of roentgen ray dermatitis. The present lesion began nine months ago and is situated on the inner dorsal surface of the right hand. It is annular and measures 3.5 cm. in diameter. The central area is free, and the surrounding border is elevated and infiltrated; the border is studded with fine, discrete, pinkish papules. There is a similar, smaller lesion on the left index finger. There are no subjective symptoms.

The patient has had diabetes for six years. The blood sugar level on October 1 was 186 mg. per hundred cubic centimeters. The urine was normal.

The patient has received four treatments with roentgen rays, totaling 300 r, and two intravenous injections of gold sodium thiosulfate, 10 mg. per dose. The lesions show about 50 per cent improvement.

DISCUSSION

DR. V. PARDO-CASTELLO, Habana, Cuba (by invitation): All of us noticed the deep infiltration and the somewhat yellowish color of this infiltrate when the skin was devoid of the superficial erythema, that is, when the blood was forced out of the capillaries by pressure on the skin. Because the patient has a high blood sugar level, I thought of the possibility of necrobiosis lipoidica diabeticorum. Of course, without a biopsy the diagnosis is tentative.

DR. MEYER L. NIEDELMAN: When the patient was first seen, the lesion seemed typical of granuloma annulare. It is a bit altered now, owing to the roentgen therapy. There is no destruction of tissue, such as is seen in necrobiosis lipoidica diabeticorum.

DR. MORRIS MARKOWITZ: On the index finger of the right hand there is a bizarre, apparently bullous eruption. Could this be a new disease, granuloma annulare bullosum?

Dermatitis Herpetiformis. Presented by DR. CARROLL S. WRIGHT and DR. MEYER L. NIEDELMAN.

W. A., a white man aged 50, of good general appearance, presents scattered over the chest, gluteal areas and legs grouped excoriations, which are ruptured vesicles. There are lesions on the scalp, scrotum and penis. There is none in the mouth.

DISCUSSION

DR. CARROLL S. WRIGHT: This case is presented, not as unusual, but as a fairly typical example, I believe, of this disease for the purpose of instigating a

discussion of its therapy. For many years it was thought that one drug had a more or less specific action on this dermatosis, i. e., solution of potassium arsenite U. S. P., or some other preparation of arsenic. Recently, fairly good temporary results have been obtained with sulfapyridine. Failures also occur.

DR. MEYER L. NIEDELMAN: I recently had a patient with dermatitis herpetiformis (gestational type), which began about the seventh month of her pregnancy. She was given injections of about 3,000,000 units of penicillin, without any effect. The eruption persisted for five months after the baby was born and then disappeared.

DR. DONALD M. PILLSBURY: My experience is confined to 1 case, but so far as my observation goes, penicillin therapy was a complete failure.

DR. MARJORY K. HARDY: I have recently seen 2 cases in which penicillin was given, with no improvement.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: Theoretically, penicillin is not indicated. Good results are obtainable with sulfapyridine.

DR. DONALD M. PILLSBURY: I recall a discussion at the Royal Society of Medicine during which Barber emphasized that sulfapyridine is superior to the other available sulfonamide drugs in treatment of dermatitis herpetiformis. I think he also stated that he kept many of his patients on small doses of sulfapyridine for a long period.

DR. HERMAN BEERMAN: How was the diagnosis arrived at? Superficially, the eruption resembles the scratch dermatitis seen with pediculosis corporis.

DR. E. R. GROSS: My colleagues and I had a patient whom we treated with 2,400,000 units of penicillin, without any effect. We have also seen patients with dermatitis herpetiformis treated successfully with one sulfonamide drug but intolerant to another. After treatment is changed to the use of sulfapyridine, they get along well. I believe that there is a neurogenic element in dermatitis herpetiformis. This patient had an exacerbation following a neurogenic upset.

DR. ISADORE ZUGERMAN: Virus infection should be considered a cause of dermatitis herpetiformis.

DR. DONALD M. PILLSBURY: Evidence has been brought on that point by Urbach. I do not believe it has ever been confirmed entirely, and further study is needed.

Cushing's Adrenogenital Syndrome. Presented by DR. MEYER L. NIEDELMAN.

M. H., an unmarried Negro woman aged 20, presents generalized hirsutism, more evident on the masculine bearded areas, which necessitates shaving daily. The patient has previously been more obese than at present and has a broad face, thick neck and heavy shoulders. The hips are broad. She has a male escutcheon. The clitoris measures about 1 inch (2.5 cm.) in length, and the vulva is atrophied. The patient's grandmother had hirsutism of the chin. The patient had the usual diseases of childhood. She first noticed a growth of hair on the chin, face and pubic region at the age of 7 years. This gradually became generalized as she grew older. She was overweight from the age of 7 to 19 years. Menstruation began at the age of 17 and has been irregular or delayed, recurring at three month intervals. The flow is scanty. There is no dysmenorrhea. She also has severe headaches.

The blood pressure is 114 systolic and 60 diastolic. The heart and lungs are normal. The visual fields and eyegrounds are normal. Pelvic examination reveals no abnormalities. The breasts are normal. Libido is normal.

Chemical studies of the blood, urinalysis and a complete blood count gave normal results. Serologic examination of the blood for syphilis gave negative results. A roentgenogram of the sella turcica revealed nothing abnormal. Perirenal roentgenographic studies after injection of air showed a normal condition. The patient was operated on in August 1945, and both adrenal glands were observed to be small and atrophic. Biopsy of a specimen of one adrenal gland revealed atrophy and sclerosis of the cortex. The ovaries and tubes were normal.

DISCUSSION

DR. MEYER L. NIEDELMAN: In a recent report of 33 cases of hirsutism, there were 4 cases of atrophy of the adrenal glands. This abnormality was designated as Cushing's adrenogenital syndrome. This case fits perfectly into that group. Therapy has been valueless in such cases.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: Schamberg used to cite the case of a woman who had ovaries and testes, and when her ovaries were removed the hirsutism cleared up.

DR. FRED D. WEIDMAN: Perhaps the explanation of that is that when destruction of the adrenal tissues has proceeded sufficiently (without rapid destruction, as in tuberculosis) there is a compensatory hypertrophy of the normal chromaffin tissue elsewhere in the body, such as that in front of the vertebrae. Normally there are little cords of chromaffin tissue there, even extending as far upward as the line of the coronary vessels. That was determined many years ago in connection with cases of complete tuberculous destruction of the adrenal glands, and yet the patients did not have a deficiency of the adrenal glands.

Larva Migrans. Presented by DR. CARROLL S. WRIGHT and DR. E. R. GROSS.

R. J., a white boy aged 2 years, has typical lesions over the flexor and dorsal surfaces of both wrists. The eruption began one month ago. Two days previously he had been playing in a sandpile near his Florida home. The sandpile was frequented by dogs. The child is being treated with fuadin, 2 cc. given intramuscularly every three days. He has had fifteen injections to date.

DISCUSSION

DR. E. R. GROSS: Treatment with fuadin is not the therapy of our choice. The physician referred the patient to us for continuation of the fuadin therapy. The child has had fifteen injections, with no improvement. With a few lesions we used ethyl chloride, with pronounced improvement.

DR. D. M. SIDLICK: What advantage is there in treating this disease with fuadin rather than with ethyl chloride? My personal experience is limited, but two or three years ago I presented a case in which only two or three treatments with ethyl chloride were required to eradicate the disease. The woman had an extensive eruption, involving not only the hand but the forearm as well.

DR. FRED D. WEIDMAN: In cases in which there are hundreds of lesions, like those that I saw in Jacksonville, Fla., it would be a long process to use ethyl chloride on every one of the lesions. Moreover, it is generally known that the first application does not catch the parasite. It might prove that in such cases fuadin would be preferable.

DR. V. PARDO-CASTELLO, Habana, Cuba (by invitation): In cases in which there may be hundreds of larvae the best treatment is solid carbon dioxide, not the kind used in offices and hospitals, but the industrial product, the kind that comes with ice cream in the form of a cake. It is applied on the surface every other day without pressure.

Keratosis Palmaris et Plantaris (Epidermodysplasia Verruciformis?). Presented by DR. PATRICIA DRANT.

M. P., a white woman aged 31, first noticed thickening of the skin on the palms and soles at the age of 8 years. Discrete, verrucous lesions appeared on the dorsa of the hands when the patient was 13 years of age. Five years ago numerous keratotic and verrucous lesions, associated with pigmentation, appeared on the neck and forehead, particularly about the hair line. Verrucous lesions appeared on the legs in August 1943, a month after confinement. These lesions began as "running sores." The patient's 2 children were presented with her. A son, born in April 1935, first had lesions on the palms and soles when he was 7½ or 8 years of age.

A daughter, born in May 1936, presented lesions simultaneously on the palms and soles at the same age.

DISCUSSION

DR. MEYER L. NIEDELMAN: This case fits into the picture of epidermodysplasia verruciformis. It is rather typical. This patient will have to be watched for the development of epithelioma, which occurs in a certain proportion of cases of this disease. I think a biopsy will confirm the diagnosis of epidermodysplasia verruciformis.

DR. DONALD M. PILLSBURY: I had the feeling that the possibility of Darier's disease (keratosis follicularis) should be considered in the mother.

DR. MARJORY K. HARDY: Has any one seen the two diseases together?

DR. MEYER L. NIEDELMAN: Epidermodysplasia verruciformis is a nevoid dyskeratosis, but not an avitaminosis. This condition does not respond to vitamin A therapy. Because of the configuration of the lesions on the body and the prominent keratoses of the palms and soles, I believe that the mother has Darier's disease (keratosis follicularis) in addition to epidermodysplasia verruciformis. The two diseases have been reported in the same patient.

Lupus Erythematosus. Presented by DR. PATRICIA DRANT.

W. H. M., a white woman aged 47, in February 1944 visited in Florida. She was physically and nervously exhausted. Her hair started to come out badly at this time. She states that she had always been subject to sun poisoning, even on moderate exposure to the sun, the reaction being characterized not only by erythema but by a pruritic, papular eruption. She had such a reaction, probably slightly severer than usual, during the two weeks she was in Florida. Two weeks after her return she broke out on both cheeks and the right ear with an erythematous eruption, apparently similar to the one now present on her left cheek. She sought treatment from a specialist immediately. She was first given one injection of a gold preparation, to which she had considerable reaction. This therapy was discontinued, and she was given a series of injections of a bismuth compound. Later she was given smaller doses of a gold preparation, to which she responded more favorably. She was discharged in February 1945. In July she had an acute recurrence.

A complete blood count on Sept. 5, 1945 revealed 72 per cent hemoglobin, 4,250,000 erythrocytes, 4,000 leukocytes, 70 per cent segmented polymorphonuclear cells, 26 per cent lymphocytes and 4 per cent stab forms. The Kolmer and Kline reactions of the blood were negative.

Biopsy was reported on by Dr. Fred D. Weidman as follows: "The epidermis was atrophic, with absence of interpapillary pegs. The only abnormality in the corium consisted of hyperplasia of the cells in the sheaths of the hair follicles. These were strictly confined to the hair follicles; i. e., they did not infiltrate the surrounding parts. These cells were more closely crowded than normal, and the nucleus was of young and proliferative type. This has led to enlargement of the hair follicle and a certain amount of distortion of its form." In the summer of 1945 the patient was given quinine sulfate orally and local applications of iodine and a sun screen cream, without result.

DISCUSSION

DR. E. R. GROSS: Dr. Carroll Wright and I have observed this patient for over a year, and it is our opinion that the lesion belongs under the head of Darier-Roussy sarcoid. She responded favorably to therapy but has had remissions and exacerbations. When her general health improved, she gained weight. When she had a nervous upset, she lost considerable weight and the lesions reappeared. The patient was given injections of gold sodium thiosulfate and also of liver extract. We felt that the only way we could produce improvement in the eruption was to improve her general health.

DR. PATRICIA DRANT: There was a time—when I took the biopsy specimen which Dr. Weidman studied—when I thought from its clinical aspect that the eruption might be granuloma annulare.

DR. MORRIS MARKOWITZ: Histologically the picture is not that of sarcoid or lupus erythematosus. The lesion has elevated borders not unlike erythema elevatum diutinum perstans. On palpation one senses an increase in local temperature. I think the lesion is a form of erythema elevatum diutinum perstans.

DR. FRED D. WEIDMAN: I do not think it is that. I do not believe that the section explains all the infiltration one can detect by palpation of the ring. It is a deep infiltration; yet the only pathologic changes I could see in the section were those in the hair follicles. I shall cut through the rest of the paraffin block so as to catch anything there is in it. This case recalls one that Dr. Corson presented many years ago at a meeting of the American Dermatological Association, concerning which there was no agreement on the diagnosis. In this case the ring was back of the ear. Three or four weeks later Dr. Wise said to me: "This is a case of porokeratosis, about which we have had so many discussions in the society." Gilchrist thought that the lesion was tuberculosis because there were giant cells in the infiltrating part. The center was atrophic, just as in the present case.

DR. PATRICIA DRANT: The skin looks normal to me. I do not think the center of the lesion is atrophic.

DR. FRED D. WEIDMAN: It is a peripherally spreading process. I feel that one would see more if one got down into the subcutaneous fat.

DR. E. R. GROSS: The type of lesion is always the same.

DR. FRED D. WEIDMAN: I do think it is lupus erythematosus.

DR. DONALD M. PILLSBURY: This case is representative of a group of cases with sensitivity to sunlight in which the eruption appears like lupus erythematosus. It is difficult at times to classify such cases accurately.

DR. FRED D. WEIDMAN: There is a group of spreading annular eruptions, including erythema chronicum migrans of Lipschütz and this wandering gyrate eruption. Erythema figuratum perstans of Wende is another. I think that the eruption in the present case is chronic erythema multiforme.

Lichen Planus (Lichen Ruber Moniliformis?). Presented by DR. JOHN W. LENTZ.

P. T., a white girl aged 19 years, presents a papular dermatosis tending to linear configuration, especially on the forearms, and limited to the arms and legs. It has been present for two years. The lesions have remained unchanged with treatment. The patient has received injections of bismuth subsalicylate intramuscularly.

DISCUSSION

DR. FRED D. WEIDMAN: I think the sections exclude lichen planus. The appearance is more that of lichen nitidus.

DR. ISADORE ZUGERMAN: I suggest that a roentgenogram of the chest be taken and the blood sedimentation rate determined. I have in mind the possible diagnosis of lichen scrofulosus.

DR. FRED D. WEIDMAN: The sections exclude that.

DR. JOHN W. LENTZ: As I was not sure what it was, I presented this case with a questionable diagnosis of lichen planus or lichen ruber moniliformis. I wonder whether Dr. Weidman has seen any section of lichen ruber moniliformis.

DR. FRED D. WEIDMAN: I remember that the lesions in the cases of Wise were not violaceous; they were white. In lichen planus there is a definite hyperplasia of cells in the epidermis, and, of course, the interpapillary pegs give a saw-toothed effect. There is a zone of lymphocytes in this area. In the present case there is, to be sure, the zone of lymphocytes, but the processes in the epidermis are not hyperplastic. If anything, they are atrophic.

DR. LOUIS GOLDSTEIN: The lesions lack the color of lichen planus and are too large for lichen ruber moniliformis. I noticed the presence of the Koebner phenomenon in the place where the biopsy was performed.

Pustular Syphilis. Presented by DR. JOHN W. LENTZ and DR. MEYER L. NIEDELMAN.

M. S., a white woman aged 41, was first seen on Sept. 26, 1945. She had been bitten on the lower lip by her boy friend about three months previously. The latter had no apparent lesions on the skin or in the mouth. The lesion appeared first as a simple fissure, but later became elevated, forming a hard mass, with no pain. Submaxillary adenopathy then developed. About six weeks after the first appearance of this lesion, multiple lesions developed, beginning on the face and extending to the neck and trunk. On admission the patient had rather extensive pediculosis capitis, and the ova are still present. Distributed over the face, neck and trunk are numerous papules, nodules and pustules. Many of the pustules have large, brownish crusts. Many of these lesions are on an erythematous base. None is painful. In the midline of the lower lip there is a crust that is the remains of the previous chancre.

On October 3, the Kolmer reaction of the blood for syphilis was 4 plus and the Kahn reaction 2 plus. The urine was reported as normal. A complete blood count gave values within normal limits.

The patient received 50,000 units of penicillin every three hours for a total of 2,500,000 units. The eruption is decidedly improved.

DISCUSSION

DR. D. M. SIDLICK: I could not see any frank pustular lesions. Some of the lesions on the body are rupial in character, and on the face they are large, flat nodules rather than pustules. One lesion on the neck presents all the characteristics of a granuloma. I think the eruption is a lesion of precocious tertiary syphilis.

DR. MEYER L. NIEDELMAN: The lesion on the lip was a typical chancre. At the time we saw the lesions they were definitely pustular, but it must be remembered that the patient has had 2,500,000 units of penicillin and that the lesions, of course, have undergone involution and what one sees now is of a rupial character.

DR. JOHN F. WILSON: It has been noted that the serologic reactions were not strongly positive. I wonder whether Dr. Niedelman could explain that.

DR. HERMAN BEERMAN: When arsenicals were used more extensively, a patient of this type would have been termed treatment resistant, and the low titer of the serologic reaction would be entirely in keeping with this. I think that even today she should be watched for the possibility of resistance to treatment.

DR. SIMON KATZ: It occurs to me that a 2 plus reaction could be a zone phenomenon. Occasionally in cases of early syphilis one gets a positive complement fixation and a negative or doubtful flocculation reaction, until one carries out a titer determination and finds that the reaction is positive in high titers and doubtful or negative in low titers. It would be interesting to see what this patient's flocculation reaction is.

DR. FRED D. WEIDMAN: There is a patch of follicular keratosis over the chest. Might this be Darier's disease (keratosis follicularis)?

DR. MEYER L. NIEDELMAN: The patient said that she has had that patch for many years.

DR. HERMAN BEERMAN: Are the lesions areas of seborrheic keratosis?

DR. FRED D. WEIDMAN: I do not think so. These are perifollicular.

Trichotillomania. Presented by DR. H. H. PERLMAN.

R. L., a white girl aged 7 years, when 2 years of age acquired the habit of playing with the hair of her scalp and twisting the hair with her fingers. At that time she did not pull her hair. The child persisted in this habit until the age of 5 years and practiced it continually in spite of reprimand, scolding and spanking. Later, hair pulling occurred at any time during the day. The child is a good

sleeper; her appetite is good, and she is not constipated. She does not receive medication of any kind and has experienced no nervous tantrums. There is no vomiting or other suggestion of nervousness. There is no evidence of masturbation.

The child was born after normal delivery at full term; she was breast fed for one month and then bottle fed. She had her first tooth at 8 months, walked at 10 months and talked at 14 months of age. She has had several attacks of bronchitis; she had chickenpox and measles at 2½ years, rubella at 6 years and whooping cough at 3½ years. She received diphtheria toxoid in infancy. A Schick test was performed months later, with a negative report. She was vaccinated during infancy and had immunizations against scarlet fever and whooping cough (Sauer vaccine).

She has received cod liver oil and vitamin C in the form of orange juice since infancy. No intestinal parasites have been noted in the stools. Her present height is 48½ inches (123 cm.) and her weight 46½ pounds (21 Kg.). This is 9 pounds (4.1 Kg.) underweight. Physical examination showed nothing abnormal except for malnutrition and partial alopecia in the occipital and parietal areas of the scalp.

The urine was normal. A complete blood count revealed 96 per cent hemoglobin (14.5 Gm. per hundred cubic centimeters), 4,800,000 erythrocytes, 72 per cent leukocytes, a color index of 1, 40 per cent polymorphonuclear leukocytes (segmented forms 39, stab forms 1), 44 per cent small lymphocytes, 5 per cent eosinophils and 2 per cent monocytes. The erythrocyte and differential white cell counts were within normal limits.

The patient has a brother aged 4½ years, who is living and well. One sister died five years ago as a result of lead poisoning. Both parents are living and well.

DISCUSSION

DR. H. H. PERLMAN: I thought there might be a frustration problem behind the behavior in this case and questioned the father and mother independently, without result. I am tempted to use an impervious dressing over the scalp.

DR. THOMAS BUTTERWORTH, Reading, Pa.: I suggest giving the child a close haircut, down to actual baldness. I have found that eventually such children cease pulling their hair out.

Calcified Sebaceous Cysts; Lupus Erythematosus of the Face. Presented by DR. E. R. GROSS.

G. S., a white woman aged 60, undernourished and seeming older than her calendar age, presents discrete, erythematous, scaly lesions on each cheek. Multiple nodular, yellowish and firm lesions are present on the fingers and at the base of the palms; these secrete a sebaceous material. The disease had its onset in 1935 as "bumps on the fingers" and became progressively worse with the development of new lesions. Two years ago an eruption developed on the face.

Physical examination revealed no gross abnormalities.

A complete blood count was essentially normal. The calcium and cholesterol contents of the blood were 11.5 and 210 mg., respectively, per hundred cubic centimeters. The urine was normal.

The patient has been treated with sodium bismuth triglycollamate ("bistrimate tablets") for the lupus erythematosus since Oct. 5, 1945, with pronounced improvement, and parathyroid injection U. S. P., 100 units, twice a month for six months.

DISCUSSION

DR. V. PARDO-CASTELLO, Habana, Cuba (by invitation): I agree with the diagnosis of lupus erythematosus of the face and the diagnosis of calcium deposits, but the diagnosis of sebaceous cysts with the calcium deposits would have to be proved. For lesions in some places on the palms, I do not think the diagnosis would stand. Biopsy is indicated.

DR. D. M. PILLSBURY: It is my impression that acrosclerosis is present.

DR. E. R. GROSS: When I first saw this patient, about eight months ago, I thought she had scleroderma. All the involved regions were calcified and stony hard. After four months of treatment with parathyroid injections the lesions softened, and I was able to express sebaceous material from many of them. A roentgenogram of the hands revealed no involvement of the long bones. A few weeks ago I prescribed the use of soluble bismuth (bistrimate), and the lesions on the face have improved about 70 per cent. This diagnosis is a tentative one. I should like therapeutic suggestions.

DR. HERMAN BEERMAN: There is a form of scleroderma associated with calcinosis, the so-called Thibierge-Weissenbach syndrome.

DR. PATRICIA DRANT: I think a chemical analysis of the expressed material should be made.

DR. FRED D. WEIDMAN: Many of us recall a case of steatocystoma multiplex presented before this society in which there was a mixture of gritty material. Considerable discussion arose as to the composition of this material. If Dr. Gross were willing to substitute the word "greasy" for "sebaceous," it would answer some of the objections that have been raised. These lesions are deep and can extend into the subcutaneous fat which is abundant on the palms, and it might be that it was this fat that was expressed. One can easily examine the gritty material to settle the question whether it is calcium or something else by adding a 10 per cent solution of sulfuric acid and placing a cover slip over it. If the cover slip bubbles up, the presence of calcium carbonate is indicated.

DR. MORRIS MARKOWITZ: A determination of the calcium and phosphate content is important. Even if the serum calcium is abnormal, the presence of calcinosis is not proved. I do not know whether the ratio between the calcium and the phosphorus has been determined in this case. An increase in the phosphorus level is usually associated with calcinosis cutis.

DR. JOHN F. WILSON: I recently saw a lesion strongly resembling the lesions on the finger of this patient. Microscopic examination revealed xanthomatous giant cell development in the tendon sheath. Though tumors may appear in a case of long standing, other changes secondary to the original tumor may develop.

DR. FRED D. WEIDMAN: Many years ago Pollitzer presented a case of calcareous change in a xanthomatous lesion.

DR. THOMAS BUTTERWORTH, Reading, Pa.: Was the test for cholesterol made after the patient had been on a low fat diet for two weeks?

A Case of Bowen's Disease. Presented by DR. M. H. SAMITZ.

E. S., a white man aged 78, presents a single patch 7.5 by 5 cm. on the anterior aspect of the left foot. The border is slightly elevated. The skin is thinned over a red-brown base, which shows through in several small, erosive areas as granulation-like tissue. The eruption is of ten years' duration.

General physical examination revealed no gross abnormalities.

The histologic report on the biopsy, by Dr. Fred D. Weidman, was as follows: "In the section which represented one-half the specimen nothing diagnostic appeared. In the other half, however, there were parts of this highly acanthotic and hyperkeratotic epidermis which exhibited the features of Bowen's disease. Thus, so far as judgment would permit (only a part of the entire thickness of the epidermis was included for study), the basement membrane was intact, but the epidermal cells were neoplastic. Their nuclei in general were large and hyperchromatic; in addition, there were numerous cells which could be classified as Bowen's cells. In keeping, too, with Bowen's disease was the fact that there was an abundant lymphocytic infiltration of the corium."

Paste of resorcinol was prescribed as a palliative until the lesion could be treated by electrocoagulation.

DISCUSSION

DR. THOMAS BUTTERWORTH, Reading, Pa.: Without a biopsy, I should consider the eruption lichen planus.

DR. MEYER L. NIEDELMAN: I suggest roentgenotherapy rather than electrocoagulation, since healing will be slow at the patient's age.

DR. BERTRAM SHAFFER: What effect would solid carbon dioxide have?

DR. CARROLL S. WRIGHT: It is the ideal means of treatment, but it would make the patient uncomfortable for some time. I should not want to do that to a patient 78 years of age.

Disseminated Lupus Erythematosus Treated with Sodium Bismuth Triglycollamate ("Bistrimate Tablets"). Presented by DR. CARROLL S. WRIGHT and DR. E. R. GROSS.

F. K., a white woman aged 38, was first seen on March 5, 1945, with disseminated lupus erythematosus involving the chest, forearms and lips, which had been present for six months. However, the onset dated back to August 1941, at which time the eruption followed a sunburn. Since then she has had remissions and exacerbations but has never been entirely free of the lesions.

At the onset she was hospitalized, had complete laboratory studies, which revealed nothing significant, and received one injection of a bismuth compound, which apparently aggravated the existing eruption. She is presented to show the pronounced improvement of the lupus erythematosus with sodium bismuth triglycollamate therapy, which was started on March 5, 1945, with 2 tablets (410 mg. each) three times a day, after meals. This is the first time that she has been relatively free from her lupus erythematosus. She is feeling much better generally. No reactions were encountered with this therapy. Thiamine chloride, 10 mg., has been given subcutaneously as a placebo at two week intervals, to keep the patient under observation.

DISCUSSION

DR. HERMAN BEERMAN: Have you control cases treated with sobisminol mass?

DR. CARROLL S. WRIGHT: We have treated about 40 patients with syphilis, about 77 with lupus erythematosus and a few with other dermatoses with this preparation. The response in patients with lupus erythematosus has been remarkable throughout, though a few could not tolerate it and we had to discontinue its use.

DR. E. R. GROSS: Sodium bismuth triglycollamate has a complex formula and was intended primarily for syphilitic therapy. Patients have now received this therapy for four or five months. It has been characterized by the absence of reactions except for bismuth stomatitis. We have seen no signs of renal irritation; there has been a daily excretion of 2 to 4 mg. of bismuth in the urine. We have not seen any fixed eruption. However, gastrointestinal disturbances with anorexia, and perhaps nausea and vomiting, have occasionally appeared at the beginning; but if the patient continues to take the drug, this complication is soon overcome, perhaps by cutting down the dose or sometimes by discontinuing the use of the drug temporarily. We believe that the good results are due to its being soluble orally and in large measure readily absorbable. Sodium bismuth triglycollamate differs from sobisminol mass.

DR. THOMAS BUTTERWORTH, Reading, Pa.: The fact that this drug is effective by mouth while other bismuth preparations are ineffective by intramuscular injection suggests that the intestine is the source of the photosensitizing agent in lupus erythematosus. The disease is of unknown origin, but administration of the bismuth directly into the intestinal tract may accomplish more than injection.

DR. CARROLL S. WRIGHT: I think that Dr. Butterworth's suggestion is a good one and that the results with this drug may give a clue to the cause of lupus erythematosus.

Keratotic Lupus Erythematosus Treated with Sodium Bismuth Triglycollamate ("Bistrimate Tablets"). Presented by DR. CARROLL S. WRIGHT and DR. E. R. GROSS.

M. C., a white woman aged 24, had a keratotic lesion of lupus erythematosus over the bridge of the nose and a discoid patch of lupus erythematosus on the left cheek, of two years' duration. These lesions were said to have followed a burn with bacon grease. Treatment with sodium bismuth triglycollamate was started on Sept. 25, 1945, with 2 tablets (410 mg. each) three times daily, after meals. She also received 0.25 cc. of liver extract subcutaneously at weekly intervals. She is presented to show the decided improvement following oral therapy with sodium bismuth triglycollamate.

DISCUSSION

DR. CARROLL S. WRIGHT: In all fairness, I must say that this patient was permitted to rub petrolatum into the crusted area, which probably removed part of the crust. She came in with a heavy scale, which quickly came off, and that alone would have produced decided improvement in her appearance. However, the lesions are undergoing involution.

Disseminated Lupus Erythematosus Treated with Sodium Bismuth Triglycollamate. Presented by DR. CARROLL S. WRIGHT and DR. E. R. GROSS.

E. B., a white woman aged 26, was first seen with disseminated lupus erythematosus of the face, chest, back and forearms, which had its onset in March 1945. On August 22 she was given a bismuth preparation parenterally, without apparent improvement. On September 10 treatment was started with sodium bismuth triglycollamate, 2 tablets three times daily, after meals. The eruption has shown decided improvement since this therapy was instituted. Liver extract, 0.25 cc., was given subcutaneously as a placebo while the patient was being treated with sodium bismuth triglycollamate.

DISCUSSION

DR. E. R. GROSS: Before this patient came to see us, she had been confined to bed with increase in temperature and painful joints. At the time she came to the office she still had a slight elevation of temperature. We felt that she had disseminated lupus erythematosus and started treatment with injections of a bismuth compound, without apparent improvement. She was then given sodium bismuth triglycollamate, and the lesions underwent involution after a week's treatment. The back and lips were involved, but are now entirely clear.

DR. DONALD M. PILLSBURY: This woman presents a characteristic picture of acute disseminated lupus erythematosus. She appears ill. I doubt whether she will live a year.

DR. CARROLL S. WRIGHT: That is the type of case, I admit, in which there is not much hope. I agree with you that she may die within a year.

NOTE (Dr. Carroll S. Wright).—One month after the presentation of this patient she had a severe recurrence. She then left the city, and nothing further has been heard from her.

Book Reviews

Allergy in Practice. By Samuel M. Feinberg, M.D., with the collaboration of Oren C. Durhan and Carl A. Dragstedt, Ph.D., M.D. Second revised edition. Price, $10.50. Pp. 838, with 35 illustrations. Chicago: The Year Book Publishers, Inc., 1946.

This book is a presentation of the subject of allergy with an attempt to cover the field and to emphasize its practical aspects. The first edition was published in 1944, but the author feels that a second edition is justified because of the recent progress in experimental and clinical fields of allergy.

There are thirty chapters beginning with an introduction and a history, anaphylaxis, hypersensitiveness in man, general causes of allergic disease and epidermal allergens. There follows a complete chapter by Oren C. Durham, Chief Botanist of Abbott Laboratories, on pollens and pollen allergy covering one hundred and four pages with photographs of the important plants producing pollen allergy and charts of their geographic distribution. The chapter on allergy to fungi is unusually thorough, largely because of the author's interest and work in this field. In the following chapters, miscellaneous inhalants, food allergy, allergy to drugs, allergy to injected substances, internal allergens and allergy to physical agents are treated. Chapters on asthma, hay fever and the treatment of allergic diseases and a chapter on hyperesthetic rhinitis cover two hundred and thirty-nine pages. The subjects which should be of most interest to the dermatologist are found in the next three chapters comprising sixty-nine pages. These are urticaria and angioneurotic edema, atopic dermatitis and dermatophytosis and contact eczema. There follow chapters on allergy of the digestive tract, migraine and allergic headaches, allergy of the eye and miscellaneous manifestations and an important chapter on preparation of allergens. The next chapter is on histamine in anaphylaxis and allergy by Carl A. Dragstedt, Professor and Chairman of the Department of Pharmacology, Northwestern University Medical School. In the final chapter, on histamine antagonists, the newer drugs "benadryl hydrochloride" N. N. R. (dyphenhydramine hydrochloride) and "pyribenzamine hydrochloride" N. N. R. (tripelennamine hydrochloride) are discussed.

Until one arrives at the chapter on atopic eczema and dermatophytosis one is impressed by the author's sincere attempt to present the subject of allergy in a clear manner and by his conservative handling of controversial subjects. Obviously, there are statements or implications with which some may be expected to disagree. For instance, it is doubtful whether the majority of dermatologists will agree with this statement, on page 659: "In spite of the present unsatisfactory status of skin tests in urticaria, I believe that in difficult and recurring cases they are justified because of the possibility that positive reactions, when they do occur, may be the means of arriving at a practical and rapid solution of the problem." The author had previously correctly stated that in his experience cutaneous tests are of value in only a small percentage of cases of urticaria. Also, the following statement regarding the beneficial effects of the injection of fungous extracts for the treatment of dermatophytosis is contrary to the belief of those who have had wide experience in this field. "I believe that desensitizing doses, given with caution, can accomplish some good. I have the impression that patients who show an immediate reaction are particularly likely to be benefited."

The chapter on atopic dermatitis and dermatophytosis comprises twenty-one pages. One wonders why these two subjects should be included in the same chapter. Many will disagree with the opening sentence of this chapter: "Atopic dermatitis is a skin inflammation of an allergic nature and of internal origin."

The following statements will likewise not be generally accepted by those having experience with patients with atopic dermatitis: "Generally, these fluctuations in intensity are due to changes or modifications of the allergic substances to which the person is exposed." "Food allergy in atopic dermatitis is common." "After the history is obtained, it is usually necessary to perform diagnostic skin tests. The procedure of choice is the scratch test." "Contrary to opinions held in some quarters, I am definitely of the opinion that desensitization treatment in atopic dermatitis should be considered as seriously as it is in allergic respiratory tract manifestations." It is the opinion of the reviewer that the author, when his theories regarding this subject are so contrary to the theories of almost all dermatologists with experience, should have presented not only his own views but also the views of the majority of workers in this field. Thousands of patients of all ages, from infancy through adulthood, with atopic dermatitis have been tested with as many as several hundred scratch tests each; many show no reaction whatever. In patients who do show positive reactions the elimination or avoidance of the suspected agent and the attempts toward desensitization have seldom resulted in any alleviation of atopic dermatitis. Why, in the light of the experiences of others and of our present knowledge, should the indiscriminate testing of these patients be further encouraged?

While the value of carefully determining the history in all phases of allergic conditions is repeatedly emphasized, even further emphasis of this extremely important procedure in the investigation of allergic conditions would be of value particularly as it relates to contact dermatitis.

While there is considerable disagreement regarding the relationship between allergy and emotional disturbances, most observers will agree with the author's statement, "A personality change in an allergic person is the result and not the cause of allergic symptoms. It is not denied that emotional, psychic or nervous factors modify or incite the allergic attack." One wonders whether it would not have been worth while to have devoted more space to the recognition and attempted management of this phase of the allergic problem as a therapeutic procedure.

A short résumé following most chapters is a valuable asset. There is an extensive bibliography at the end of each chapter and an index which is most useful.

Penicillin Therapy and Control in the Twenty-First Army Group. Published under the direction of the Director of Medical Services, Twenty-First Army Group. Pp. 365. Printing and Stationery Service, British Army of the Rhine, 1945.

This book is a compilation of sixty reports and articles by members of the Royal Army Medical Corps, Twenty-First Army Group. It includes many subjects other than penicillin therapy, such as those dealing with the surgical treatment of war wounds. In the introduction by the consulting surgeon it is modestly titled a "brochure," but it is definitely more than "a pamphlet dealing with a subject of passing interest" because this publication is the useful result of a great amount of practical investigation carried out in the difficult circumstances arising in an active campaign

In the section devoted to the use of penicillin in the treatment of diseases of the skin, two methods of local application are described: (1) as a solution containing 200 to 500 units per cubic centimeter of sterile water and (2) as an emulsion of 30 per cent Lanette wax in water containing 200 to 500 units per gram. The solution was sprayed on the skin three times daily in the clinic, and the emulsion, when used, was applied by the patient, with equally good results in the treatment of impetigo, sycosis barbae, ecthyma and infected dermatitis of various types. In all these diseases except impetigo it was necessary to supplement penicillin with other drugs to complete the cure after penicillin had dealt with the "infective element" of the disease. The drug was found to be useful in the treatment of furuncles and carbuncles when administered parenterally.

The book should be most useful to physicians interested in the broad field of penicillin therapy in general medical and surgical diseases.

The Girls They Left Behind. By Brethe Hartmann, M.D. Price, 12 kroner. Pp. 208. Copenhagen: Ejnar Munksgaard Forlag, 1946.

This monograph presents the results of a study of the effects of the war and the German occupation on the incidence of prostitution and venereal disease in Denmark. It is based on data gathered principally in the police courts. A large number of case histories is included in which the family background, religion, education, occupation, personal interests, sex history and medical facts of individual girls are detailed.

In 1936, Tage Kemp wrote as follows: "We have made such progress in the campaign against syphilis in Denmark, and especially in Copenhagen, that we may regard the disease as an exotic malady, like cholera and smallpox, usually brought into the country by seafarers and travelers from foreign lands." Unfortunately, this roseate situation did not last long. After the German occupation in April 1940 the prevalence of syphilis increased rapidly, so that in 1944 it was 8.3 times that in 1938.

In 1939, the women examined in the police courts were almost exclusively professional prostitutes, and 15 per cent were infected with venereal diseases. However, in 1943, as a result of war, overcrowding, family dislocations, German occupation and other factors, the girls examined belonged to younger age groups and were chiefly of nonprofessional status, and the incidence of venereal diseases among them was 55 per cent.

The book is well written in English, but it will have greater interest for the sociologist and the epidemiologist than for the dermatologist.

Tropical Medicine. By Sir Leonard Rogers and Sir John W. D. Megaw. Fifth edition. Price, $6.50. Pp. 518, with 89 illustrations. Baltimore: William Wood & Company, 1944.

Because of the continued emphasis on a book of a short practical type of text, especially for the general practitioner, there is not a great deal of material on tropical dermatology included. The emphasis has been on tropical medicine, especially in India. The section on microscopy is of practical value. The following dermatologic diseases are considered briefly: chagomata, leishmaniasis, mycoses, tropical ulcer, ainhum, tungiasis, Hodgkin's disease, leprosy, yaws, plague, carbunculosis, pellagra, ariboflavinosis, dermatitis solaris, larva migrans and syphilis.

Because of brevity, some controversial material in regard to tropical dermatology is included. This is especially true of "espundia," in which oronasal involvement is reported to occur in some 80 per cent of the cases. This figure is unusually high except in some heavy endemic areas. Contrary to the authors, oronasal involvement as yet has not been reported in Mexico. This is another argument for discarding a confusing colloquial term in general literature such as "espundia" and substituting a clearer term such as "American cutaneous leishmaniasis with mucosal involvement, primary (or metastatic)." In regard to the search for microfilariae in onchocerciasis in America, these parasites are found easily. Follicular keratoses are not noted in the description of vitamin A deficiency. The remarks on syphilis in India are interesting in that there is a discussion of the rare complications of primary syphilitic pulmonary atheroma. Also, although it is indicated, as usual, that tabes and paresis are rare in the tropics (diagnosis?) paraplegia due to syphilis is reported as a "very common late manifestation in India." The remarks on the incidence of tumors in India as compared to London are also interesting, "malignant epithelial tumors . . . showed excess in India of epithelioma of the skin in relation with the frequency of chronic ulcerative processes." Also, epithelioma of the penis is more common in uncircumcised Hindus than in the circumcised Mohammedans. Epithelioma of the inside of the cheek often follows chewing betel nut with lime.

It is chiefly, then, the general practitioner in India who will find this small volume of definite practical value.

The Problem of Lupus Vulgaris. By Robert S. Aitken, M.D., Lecturer in Diseases of the Skin, Edinburgh University. First edition. Price, $4. Pp. 76, with 31 illustrations in color and black and white. Baltimore: Williams & Wilkins Company, 1946.

This small manual, written by a man with many years of experience in treating lupus vulgaris, is a good résumé of the author's personal experience with this disease. However, it is unfortunate that an advance in the treatment of lupus vulgaris as important as the use of vitamin D_3, reported by Charpy in 1943, was not known to the author. This new development in therapy is not referred to at all.

As a survey of what the problem of lupus vulgaris is, both to the individual and to the community, and as an evaluation of technic of treatment with special reference to the fine results obtained by the Finsen-Lomholt lamp, this book would be valuable to physicians, including general practitioners, who encounter lupus vulgaris.

The book is divided into five chapters. These chapters cover the clinical features of the disease, treatments in general, ultraviolet irradiation, tuberculin treatment and the social and economic problems of lupus vulgaris.

In the chapter on the clinical features of the disease, the characteristics of lupus vulgaris of various types are described. The author also discusses the relationship between lupus vulgaris and tuberculosis elsewhere in the body and states that lupus is rarely accompanied or followed by pulmonary tuberculosis. The geographic distribution and the age and sex incidence of lupus vulgaris are discussed, as well as the etiology, differential diagnosis and prognosis. It is said to be twice as common in women as in men. The onset is usually in childhood or adolescence, and the bovine and human tubercle bacillus in attenuated form is the responsible organism, with the focus of infection nearly always internal.

The main part of the book covers the treatment of lupus vulgaris. This is divided into three chapters, on treatment in general, on treatment with ultraviolet irradiation and on treatment with tuberculin. The Gerson salt-free diet is said to be impractical, and the use of roentgen ray is condemned. Lomholt is quoted as saying that he never saw a case of carcinoma on lupus unless there had been previous roentgen ray treatment.

The history of the development of the Finsen-Lomholt carbon arc lamp, a description of its mechanism and its faults and the general technic of its use, as well as comparison of this lamp with mercury vapor lamps, are given in the chapter on ultraviolet irradiation. Here the results of local ultraviolet therapy combined with general ultraviolet irradiation are evaluated.

The third chapter on treatment deals with the use of tuberculin in the treatment of lupus vulgaris, and excellent results are reported with either tuberculin ointment or subcutaneous injections in carefully regulated doses. Treatment with tuberculin is recommended when ultraviolet irradiation cannot be obtained.

The final chapter in the book deals with the economic and social aspects of lupus vulgaris.

Practical Handbook of the Pathology of the Skin. By J. M. H. MacLeod and Isaac Muende. Third edition. Price, $9. Pp. 416, with 27 colored and 125 black and white illustrations. New York: Paul B. Hoeber, Inc., 1946.

Strictly speaking, this is not a new edition. It is a reprint. The number of pages in the book is exactly the same, and the various topics appear on the same pages in the second as in the third edition. This edition is printed on heavy enamel stock, and accordingly the book is considerably thicker than the preceding one.

As its title indicates, the subject of pathology is discussed in all of its aspects: histologic technic, embryology, anatomy, congenital anomalies, tissue changes in disease, animal parasites, bacteriology and mycology.

The illustrations are the features that are the most needed in dermatology, and it is regrettable that the text concerning the histopathology is not more ample, but the extended scope of the book has doubtless prevented this. The book continues to be the most useful one of its kind in dermatology.

Penicillin in Neurology. By Arthur Earl Walker, M.D., and Herbert C. Johnson, M.D. First edition. Price, $5. Pp. 216, with 95 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

The authors have reviewed the literature relative to the effects of antibiotics on the central nervous system and have presented their own interesting experimental and clinical data. Major attention is given to the toxic effects of penicillin when administered parenterally, when applied directly to nervous tissue or when injected into the lateral ventricles, the cisterna cerebellomedullaris or other subarachnoid space. The therapeutic value of penicillin and other antibiotics in various infectious and noninfectious diseases of the central nervous system has been covered adequately.

Of chief interest to the dermatologist is the section devoted to the treatment of syphilis of the central nervous system. The subject is considered briefly, and it is noteworthy that not one of the twenty references in the bibliography pertain to articles published later than 1945. The tempo of investigation in neurosyphilis has been so rapid that it has outstripped the material published in this book. Reference is made to the danger of serious reactions resembling Herxheimer's reaction in the central nervous system, when therapeutic doses of penicillin are initiated and to the method of obviating such reactions.

The book is well written and profusely illustrated, but it has greater value for the neurologist and the neurosurgeon than for the dermatologist.

Allergy. By Erich Urbach, M.D., and Philip M. Gottlieb, M.D. Second edition. Price, $12. Pp. 968, with 412 illustrations. New York: Grune & Stratton, Inc., 1946.

The publication of this second edition only three years after publication of the first indicates a demand by the members of the medical profession for this book. The authors have added 21 new illustrations and 1,300 new references after omitting a few hundred older ones. New sections are added on psychosomatic aspects, the Rh factor, allergic bronchitis, allergic cough and eosinophilic erythredema. The index of authors comprises 26 pages and the index of subjects 33 pages.

The book is divided into three parts. The first deals with the fundamentals of allergy; the second, with etiologic agents of allergic diseases and the third part with symptoms and therapy of allergic diseases. The allergic diseases of the different organs and systems of the body are taken up. Almost 100 pages are devoted to cutaneous diseases.

The reviewer has paid special attention to the part relating particularly to dermatology. He is convinced that the dermatologist will find this book stimulating because of an enormous amount of interesting and important topics. This book may be used as a reference book by the general medical practitioner, but the dermatologist will profit considerably by reading this textbook from beginning to end.

Some of the personal opinions of the authors, for instance as to the value of propeptans, may be in disagreement with the opinions of most of the observers in this country. Nevertheless, it does not detract from the value of the book as the authors cite references for opinions different from their own.

INDEX TO VOLUME 55

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

Abnormalities and Deformities: See under names of diseases, organs and regions, as Atrophy; Hair, abnormalities; Nails, abnormalities; Pigmentation; Skin, abnormalities; etc.
Abramowitz, E. W.: Scleredema adultorum or scleroderma, 705
Abscess: See under names of organs and regions
Acanthosis nigricans, 291
  nigricans, juvenile, and ichthyosis, 411
  nigricans, juvenile type, 139, 144
  nigricans juvenilis associated with obesity; report of case with observations on endocrine dysfunction in benign acanthosis nigricans, *749
Acarodermatitis Urticarioides: See Grain Itch
Acarus Scabiei: See Scabies
Ace Adherent, contact dermatitis due to, 400
Acetarsone, Therapy: See Pemphigus foliaceus
Achondroplasia; atypical chondrodystrophia of type Morquio associated with follicular atrophoderma, 266
Achromia: See Pigmentation; Vitiligo
Acid, Undecylenic: See Moniliasis; Ringworm
Ackerman, L. V.: Elephantiasis neuromatosa; manifestation of von Recklinghausen's disease, *233
Acne conglobata, 284
  rosacea, 844
  rosacea or lupus vulgaris, 304
  urticata; case for diagnosis, 302
  vulgaris; case for diagnosis, 138
  vulgaris treated with vitamin A, *355
Acridine Dyes; atypical lichen planus tropicalis, *535
  dermatitis from atabrine, 550
  hyperkeratosis of palms and soles due to ingestion of quinacrine hydrochloride, *256
  lichen planus-eczematoid dermatitis complex of Southwest Pacific, 549
  quinacrine hydrochloride dermatitis; case for diagnosis, 291
  quinacrine hydrochloride dermatitis occurring during war, *453
  skin sensitivity due to atabrine, 550
  unusual dermatosis simulating lichen planus and lichen corneus hypertrophicus; report of 6 cases, *12
Acrokeratosis: See Keratosis
Actinodermatitis: See under Light
Actinomyces; search for virus-inactivating substances among microorganisms, 119
Actinomycin: See Actinomyces
Actinomycosis, 299
  Madura foot (mycetoma); first report from Isthmus of Panama, *761
Adams, J., Jr.: Dermatitis medicamentosa; case for diagnosis, 414
Addison's Disease, adrenocortical cancer with undulating fever in, 835
  chronic idiopathic hypoparathyroidism with superimposed Addison's disease in child, 835
  dyskeratosis congenita with pigmentation, dystrophia unguium and leukoplakia oris; patient with evidence suggestive of Addison's disease, *242
  in infant, 835
Adhesive Plaster; contact dermatitis due to Ace Adherent, 400
Adipose Tissue: See Fat; Obesity
Adolescence; acanthosis nigricans juvenilis associated with obesity; report of case with observations on endocrine dysfunction in benign acanthosis nigricans, *749
Adrenal Preparations; epinephrine and denervation, 403
Adrenals; adrenocortical cancer with undulating fever in Addison's disease, 835
  chronic idiopathic hypoparathyroidism with superimposed Addison's disease in child, 835
  dyskeratosis congenita with pigmentation, dystrophia unguium and leukoplakia oris; patient with evidence suggestive of Addison's disease, *242
Aeronautics: See Aviation and Aviators
Aerosol: See Ringworm
Agglutinins and Agglutination: See Antigens and Antibodies; etc.
Agranulocytosis; report of 12 cases in which it followed intensive arsenotherapy for syphilis, *57
Ainhum; etiologic concepts and pathologic aspects, 117
  pathologic findings; comparison of epidermal and vascular lesions with normal toe [in Negroes], 261
Alderson, H. E.: Chronic coccogenous sycosis treated locally with penicillin, 573
  Lichenoid dermatitis (New Guinea type), 576
Allergy: See Anaphylaxis and Allergy
Allington, H. V.: Idiopathic atrophy of the skin; case for diagnosis, 737
Alopecia areata in infants, 143
  cicatrisata; pseudopelade, 424
  marginalis, inflammatory, 724
  of undetermined cause; generalized vitiligo, 425
Altar of Isenheim: See Drawings
American Board of Dermatology and Syphilology, 115, 548, 831
Amersbach, J. C.: Granuloma annulare, sarcoid or psoriasis, 151
  Rosacea, 844
Amidines; antibacterial and fungistatic properties of propamidine, 550
Amyloidosis, primary lichen; report of necropsy, *251
Anaphylaxis and Allergy: See also Food, allergy; Tuberculosis, allergy; and under names of various diseases, as Eczema; Rhus; etc.
  allergic reaction following typhus fever vaccine and yellow fever vaccine due to egg yolk sensitivity, 400
  anaphylactic shock from skin testing; 2 cases, 1 fatal, 400
  clinical use of new antihistaminic compound (pyribenzamine) in certain cutaneous disorders, *309
  effect of turpentine oil on normal and hypersensitive skin, 703
  elimination of human reaction-producing material from horse-derived antiserums; electrical method, 118
  pathogenesis of encephalitis due to salvarsan, 264
  reaction to penicillin simulating serum sickness, 261
  use of histamine antagonist, beta-dimethylaminethyl benzhydryl ether hydrochloride, in allergic disease, 832
Anderson, C. R.: Longitudinal grooving of nails caused by synovial lesions, *828
Andrews, G. C.: Sporotrichosis or secondary syphilis [treated], 727
  Trichoepithelioma, 726

Androgens; treatment of post-traumatic Simmonds' disease with methyl testosterone linguets, 834
Anemia; epithelial symptoms caused by various deficiencies, 555
pernicious, carotenemia in patient with, 724
sickle cell, in white patients with ulcers of ankles; report of 2 cases, 833
Anetoderma: See Atrophy
Angina, Agranulocytic: See Agranulocytosis
Monocytic: See Mononucleosis, Infectious
Angioma; angiomatoid formations in genital organs with and without tumor formation, 834
angiopericytoma; case for diagnosis, 726
hemangioma, 304
of scrotum, 548
Anhidrosis: See Sweat Glands
Ankle: See also Foot
sickle cell anemia in white patients with ulcers of; report of 2 cases, 833
Antigens and Antibodies: See also Lipoids; and under specific antigens and reactions as Chancroid; etc.
cardiolipin-lecithin antigen; recent development toward single standard test of blood for syphilis, *514
specificity of serologic precipitation, 118
Antimony and Antimony Compounds, Therapy: See Creeping Eruption
Anus; tuberculosis orificialis; case for diagnosis, 409
Aphthosis: See Stomatitis, aphthous
Apparatus: Finsen treatment and significance to rational combating of lupus vulgaris, 122
Appel, B.: Nevus linearis or localized scleroderma (morphea), 716
Tuberculosis orificialis; case for diagnosis, 409
Armed Forces Personnel: See also Aviation and Aviators; Military Medicine; Naval Medicine; etc.
in military dermatology, *446
Armies: See Aviation and Aviators; Military Medicine; War
Arnold, H. L., Jr.: Hyperkeratosis penetrans; report of case of probable variant of Kyrle's disease, *633
Arsenic and Arsenic Compounds: See also Arsphenamines
agranulocytosis; report of 12 cases in which it followed intensive arsenotherapy for syphilis, *57
BAL (British Anti-Lewisite), 120
Bowen's disease or tuberculosis cutis, 418
mycosis fungoides or arsenical dermatitis, 275
psoriasis; arsenical pigmentation and keratoses; squamous cell epithelioma of finger with metastasis to axillary lymph nodes, 294
Therapy: See Creeping Eruption; Syphilis
toxic effects of arsenical compounds as administered in United States Navy in 1944, with reference to arsenical dermatitis, 262
Arsphenamines; pathogenesis of encephalitis due to salvarsan, 264
postarsphenamine vitiligo, 272
Therapy: See under Syphilis
Art: See Drawings
Arteries: See also Vasomotor System; etc.
venospasm; its part in producing clinical picture of Raynaud's disease, 399
Arthritis, rheumatoid (Still's disease) or vascularitis of unknown origin, 849
Asthma: See Anaphylaxis and Allergy
Atabrine: See Acridine Dyes
Atopy: See Anaphylaxis and Allergy
Atrophoderma: See Atrophy
Atrophy: See also Poikiloderma atrophicans vasculare; and under names of organs and regions, as Face; etc.
atrophoderma hypoestrogenicum, 148
atypical chondrodystrophia of type Morquio associated with follicular atrophoderma, 266
ichthyosiform changes of skin associated with internal diseases, *28
idiopathic, of skin; case for diagnosis, 737
of skin; peculiar form, 265
Aviation and Aviators; treatment of mycotic infections by inhibiting respiration of dermatophytes, *379
venereal disease in Army Air Forces in continental United States, 1942-1944, 697
Avitaminoses: See under Vitamins
Axilla, Lymph Nodes: See Lymph Nodes
Axon: See Neurons
Ayres, S., Jr.: Leukoderma acquisitum centrifugum, 429
Perforating ulcer of foot in 2 sisters, 430
Ayres, S., III: Pinta, 288
Superficial epithelioma of Bowenoid type, 287

Babalian, L.: Juvenile acanthosis nigricans and ichthyosis, 411
Bacillus: See Bacteria
Bacteria: See also Pneumococci; Streptococci; Viruses; etc.
Actinobacilli: See Actinomycosis
antibacterial and fungistatic properties of propamidine, 550
Calmette-Guérin: See Tuberculosis
corynebacteria; cutaneous diphtheria and tropical ulcers, *360
Diphtheria: See Diphtheria
Ducrey's: See Chancroid
effect of urea, urethane and other carbamates on bacterial growth, 119
Leprosy: See Leprosy
Pseudomonas aeruginosa infection of ear treated with streptomycin, *257
Bacterium: See Bacteria
Baldness: See Alopecia
Barker, L. P.: Dermatitis venenata or erythroplasia, 845
Giant urticaria with lymphedema, 416
Hyperkeratosis of palms and soles due to ingestion of quinacrine hydrochloride, *256
Syphilis, early tertiary, 150
Barner, J. L.: Basal cell epithelioma in psoriatic patch, *375
Barr, J. H.: Cutaneous horn, 282
Basophils: See Erythrocytes
Bauer, J. T.: Primary lichen amyloidosis; report of necropsy, *251
Bazin's Disease: See Erythema induratum
BCG: See under Tuberculosis
Bechet, P. E.: Nevus pigmentosus, 269
Beerman, H.: Parasitic infection or scabies, 597
Beeswax; penicillin in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin in single and multiple doses in isotonic solution of sodium chloride and peanut oil-beeswax by intramuscular injection, *741
Benadryl: See Eczema; Urticaria
Bentonite: See Ointments
Benzocaine: See Pediculosis
Benzyl Benzoate: See Pediculosis; Scabies
Bernhardt, E.: Dermatophytosis of face caused by Trichophyton camerounense, *337
Binkley, G. W.: Epidermodysplasia verruciformis or chronic myeloid leukemia, 280
Bismuth and Bismuth Compounds, Therapy: See under names of various diseases, as Lupus erythematosus; Syphilis; etc.
Bistrimate Tablets: See Lupus erythematosus
Blastomycosis, 561. See also Coccidioidomycosis; Moniliasis
papulopustular verrucous sporotrichosis simulating blastomycosis, 290
Blennorrhagia: See under Gonorrhea; Keratosis
Blepharitis: See Eyelids
Blisters: See Vesication
Blood: See also Erythrocytes
carotene; carotenemia, 708
carotene; carotenemia in patient with pernicious anemia, 724
Diseases: See Anemia; Leukemia
groups; hemolytic disease and congenital syphilis in siblings, 263
identification of inhibitory factor of reticuloendothelial immune serum (REIS) in globulin fraction, 261
pemphigus vulgaris; study of blood picture, *772

Blood—Continued
penicillin levels in serum and some body fluids during systemic and local therapy, 551
Bloom, D.: Chronic lymphedema of eyelids, 709
Multiple keloids in twin sisters, 426
Bockus, H.: Leukemid or scabies, 595
Body Fluids: See Fluids
Boeck's Sarcoid: See Sarcoidosis
Boil, Jericho: See Leishmaniasis
Boils: See Furunculosis
Bones: See also under names of bones
elephantiasis neuromatosa; manifestation of von Recklinghausen's disease, *233
eosinophilic granuloma of skin; its relation to erythema elevatum diutinum and eosinophilic granuloma of bone; report of case, *194
"eosinophilic granulomas" of skin, *155
eosinophilic granuloma; theoretic and practical considerations based on study of case, *176
eosinophilic granuloma with cutaneous manifestations; report of case, *810
melanotic nevus of cheek, apparently undergoing malignant degeneration, due to large underlying foreign body granuloma which has developed around bone formation, 265

Book Reviews:
Allergy; E. Urbach and P. M. Gottlieb, 868
Allergy in Practice; S. M. Feinberg, O. C. Durhan and C. A. Dragstedt, 864
Cosmetics and Dermatitis; L. S. Schwartz and S. M. Peck, 306
Diseases of Skin for Practitioners and Students; G. C. Andrews, 307
Girls They Left Behind; B. Hartmann, 866
Human Toruiosis: Clinical, Pathological and Microbiological Study, with Report of Thirteen Cases; L. B. Cox and J. C. Tolhurst, 432
Pathology of Tropical Diseases; J. E. Ash and S. Spitz, 306
Penicillin in Neurology; A. E. Walker and H. C. Johnson, 868
Penicillin: Its Practical Application; A. Fleming, 740
Penicillin Therapy and Control in Twenty-First Army Group, 865
Practical Handbook of Pathology of Skin; J. M. H. MacLeod and I. Muende, 867
Problem of Lupus Vulgaris; R. S. Aitken, 867
Skin Diseases, Nutrition and Metabolism; E. Urbach and E. B. LeWinn, 600
Treatment by Ion Transfer (Iontophoresis); D. Abramowitsch and B. Neoussikine, 219
Tropical Medicine; L. Rogers and J. W. D. Megaw, 866
Venereal Diseases in General Practice; S. Lomholt, 308

Bouillaud's Disease: See Rheumatic Fever
Bowen's Disease: See Cancer, precancer
Brain, Diseases: See Encephalitis
Syphilis: See Neurosyphilis
Breast, cancer; dermatomyositis and malignant tumor, 838
eczema or carcinoma simplex of nipple, 711
extensive Paget's disease without formation of cancer during constant observation for 14 years, 266
Brocq's Disease: See Alopecia cicatrisata
Brocq-Duhring Disease: See Dermatitis herpetiformis
Brooke-Morrow's Disease: See Keratosis follicularis
Brown, E. A.: Effects of glycerite of hydrogen peroxide on infections of skin and mucous membranes, *801
Bubo, Chancroid: See Chancroid
Climatic: See Lymphogranuloma Venereum
Buchholz, A.: Tuberculosis verrucosa cutis and tuberculosis colliquativa, 131
Buerger's Disease: See Thromboangiitis obliterans
Bullosis: See Vesication
Burns: See also Cicatrix
of face; treatment with grenz rays, 555
Buschke's Disease: See Scleroderma
Butler, M. G.: Atypical lichen planus tropicalis, *535
Buttock; granuloma inguinale involving buttock and lymph node; cultivation of Donovan body in embryonic yolk, *342

Calcification; calcified sebaceous cysts; lupus erythematosus of face, 860
generalized calcinosis, 141
Calcinosis: See Calcification
Calero M., C.: Madura foot (mycetoma); first report from Isthmus of Panama, *761
Callaway, J. L.: Pseudomonas aeruginosa infection of ear treated with streptomycin, *257
Callosities: See Keratosis
Cancer: See also Epithelioma; Sarcoma; Tumors; and under names of organs and regions, as Adrenals; Breast; Lips; Ovary; etc.
dermatomyositis and malignant tumor, 838
growth, invasive character of, 697
melanotic nevus of cheek, apparently undergoing malignant degeneration, due to large underlying foreign body granuloma which has developed around bone formation, 265
precancer; Bowen's disease, 861
precancer; Bowen's disease or tuberculosis cutis, 418
precancer; Bowen's disease (with rare localization between second and third left toe), 266
precancer; erythroplasia of glans penis (Bowen's disease of mucous membranes), 265
precancer; superficial epithelioma, Bowen's disease, roentgen ray dermatitis or neurodermatitis, 851
precancer; superficial epithelioma of Bowenoid type, 287
Cannon, A. B.: Ichthyosis hystrix or psoriasis, 268
Pityriasis rubra pilaris, 725
Postarsphenamine vitiligo, 272
Sarcoid or leprosy, 589
Capillaries: See also Vasomotor System
microscopy with reference to capillary petechiae, 832
Carate: See Pinta
Carbowax Compound: See Ointments
Carcinoma: See Cancer
Cardiolipin: See Lipoids
Cardiovascular Diseases; account of stock, 833
Cardiovascular System: See Arteries; Vasomotor System; etc.
Carnauba Wax: See Ointments
Caro, M. R.: Lupus erythematosus, 135
Lymphoblastoma, 140
Tuberculosis verrucosa cutis and tuberculosis colliquativa, 131
Carotene: See Vitamins, A
in Blood: See Blood, carotene
Carotenemia: See Blood, carotene
Cawley, E. P.: Eosinophilic granuloma of bone with cutaneous manifestations; report of case, *810
Cecum; unilateral ulceration of mouth (tuberculosis orificialis?), probably with miliary and ileocecal involvement, 580
Ceder, E. T.: Treatment of various types of cutaneous tuberculosis with promizole and streptomycin; preliminary report, *222
Cells: See also Tissue; etc.
cytology of molluscum contagiosum with significance of so-called "vacuoles," 260
pemphigus vulgaris; study of blood picture, *772
Cellulitis: See under Scalp
Cerebrum: See Brain
Chancre, Lymphogranulomatous: See Lymphogranuloma Venereum
Soft: See Chancroid
Chancroid; cause of phagedenic soft chancre, 267
Chaulmoogra Oil, Therapy: See Leprosy
Chemotherapy: See under names of diseases and chemotherapeutic agents, as Neurosyphilis; Penicillin; Sulfonamides; Syphilis; Tuberculosis; etc.
Chickenpox and herpes zoster, 263
varicella herpetiformis, 839

Children: See also Infants
chronic idiopathic hypoparathyroidism with superimposed Addison's disease in child, 835
desensitization to insect bites, 700
Chloasma: See under Pigmentation
Chlorides: See Sodium chloride
Chloroma: See Leukemia
Chondrodystrophia Fetalis Calcarea: See Achondroplasia
Christian-Weber's Disease: See Panniculitis
Cicatrix; acne conglobata, 284
ocular pemphigus with scarring of skin and mucous membranes, *37
lupus vulgaris, 149
pathologic findings in case of ainhum; comparison of epidermal and vascular lesions with normal toe, 261
Cipollaro, A. C.: Junction nevus, 583
Nummular eczema, 586
Radiodermatitis, 585
Clothing; dermatitis from glass fabrics, *258
Coal Tar: See under Skin, diseases
Coccidioidomycosis or unilateral ulceration of mouth (tuberculosis orificialis?), probably with miliary and ileocecal involvement, 580
Cockroaches; modes of transmission of Hansen's disease (leprosy), 702
Cohen, D.: Lupus vulgaris with squamous cell epithelioma, 132
Pellagra, 570
Cole, H. N.: Dermatosis, progressive pigmentary, 297
Erythema chronicum migrans, 277
Larva migrans, 296
Myoblastoma, 297
Parapsoriasis, 278
Parapsoriasis en plaque, 279
Urticaria pigmentosa (nodular type), 280
Colitis, ulcerative, skin lesions during course of, 121
Collagen; reticulum, or lattice, fibers; further studies, *478
Colon, Inflammation: See Colitis
Combes, F. C.: Contact dermatitis of hands, 276
Epidermodysplasia verruciformis, 727
Frambesiform tertiary syphilis, 840
Granuloma inguinale, 840
Lupus erythematous or pemphigus, 270
Mycosis fungoides, 271
Communicable Diseases: See Syphilis; etc.
Complement Fixation Test: See Rocky Mountain Spotted Fever; Syphilis, serodiagnosis; Wassermann Reaction; etc.
Congress: See Societies
Conjunctivitis; Stevens-Johnson syndrome (eruptive fever with stomatitis and conjunctivitis), 832
Constant, E. R.: Case for diagnosis, 302
Cook, C. D.: Acne vulgaris treated with vitamin A, *355
Coomber, R. B.: Dermatitis from contact with varnish of Japanese rifles, *110
Cooper, Z. K.: Lichen sclerosus et atrophicus with bullous lesions and extensive involvement; report of case, *433
Copper, Therapy: See Mycosis, cutaneous
Cormia, F. E.: Eosinophilic granuloma; theoretic and practical considerations based on study of case, *176
Psychosomatic factors in dermatoses; critical analysis of diagnostic methods of approach, *601
Cornbleet, T.: Dermatomyositis; case for diagnosis, 570
Lupus vulgaris with squamous cell epithelioma, 132
Lymphoblastoma; case for diagnosis, 142
Multiple superficial epitheliomatosis, 134
Pellagra, 570
Pityriasis rubra pilaris with exfoliation, 141
Subacute disseminated lupus erythematosus, 136
Unexplained fluorescence phenomenon, 564
Correction in Dr. Zakon's discussion of paper by Dr. F. R. Schmidt, "Chronic Discoid Lupus Erythematosus" (54: 744 [Dec.] 1946), 259
Corynebacterium Diphtheriae: See Diphtheria
Cosmetics; inflammatory alopecia marginalis following electric permanent wave, 724
lupus erythematosus or chloasma, 426
scientific principles in design and choice of ointment bases, 553
Costa, O. G.: Leishmaniasis verrucosa of face, *358
Tinea nigra, *67
Tuberculoid leprosy of lupoid appearance, *474
Costello, M. J.: Carotenemia in patient with pernicious anemia, 724
Case for diagnosis, 420
Dermatitis herpetiformis (papular type) successfully treated with sulfapyridine, 725
Erythema elevatum diutinum, 710
Erythema multiforme bullosum and dermatitis medicamentosa [sulfonamide compounds], 852
Erythema multiforme bullosum (due to sulfonamide medication), 853
Inflammatory alopecia marginalis, 724
Linear lichen planus, 724
Linear nevus or lichen planus atrophicus, 268
Morphea-like epithelioma and basal cell epithelioma of face cured by roentgen ray therapy, 585
Poikiloderma atrophicans vasculare; case for diagnosis, 588
Counter, C. E.: Stomatitis due to ingested medication; case for diagnosis, 126
Cranium, fractures; treatment of posttraumatic Simmonds' disease with methyl testosterone linguets, 834
Crawford, G. M.: Tertiary syphilis of skin, 413
Creeping Eruption; larva migrans, 722, 728, 856
larva migrans [treatment with fuadin], 296
systemic treatment (arsenic, antimony and fuadin), *664
Curth, H.: Generalized vitiligo; alopecia of undetermined cause, 425
Curtis, A. C.: Congenital absence of valves in veins as cause of varicosities, *639
Eosinophilic granuloma of bone with cutaneous manifestations; report of case, *810
Cushing Syndrome; Cushing's adrenogenital syndrome, 855
Cutis Verticis Gyrata: See Scalp
Cysts: See under names of organs and regions, as Sweat Glands; Sebaceous Glands; etc.
Cytology: See Cells

Dacryocystitis: See Lacrimal Organs
Dactylitis: See Fingers and Toes
Dactylolysis Spontanea: See Ainhum
Dandruff: See Seborrhea
Darier's Disease: See Keratosis follicularis
Davis, W. C.: Clinical experience with ointment of synthetic coal tar, *683
DDT: See Pediculosis; Skin, diseases
Death; account of stock, 833
Deficiency Diseases: See Pellagra; Vitamins; etc.
Denhoff, E.: Cutaneous diphtheria and tropical ulcers, *360
Dennie, C. C.: Use of Purple X bulb in diagnosis of fungous diseases of scalp, *396
Depigmentation: See Pigmentation
Dermatitis: See also Eczema; Neurodermatitis; etc.
Acneform: See Acne
Actinica: See under Light
Atopic: See Eczema; Neurodermatitis
Atrophicans: See Atrophy
Blastomycetic: See Blastomycosis
clinical use of new antihistaminic compound (pyribenzamine) in certain cutaneous disorders, *309
Contact: See Dermatitis venenata
Eczematous: See Eczema
exfoliative, possible benefit from protein hydrolysates for, *397
herpetiformis, 854
herpetiformis; case of diagnosis, 150
herpetiformis caused by stasis dermatitis, 596
herpetiformis; epidermolysis bullosa; recently described variant, *91

Dermatitis—Continued
herpetiformis or papular urticaria, 731
herpetiformis or pemphigus, 415
herpetiformis (papular type) successfully treated with sulfapyridine, 725
iodide, 305
lichenoid, 835
lichenoid (New Guinea type), 576
Medicamentosa: See also under names of drugs, as Acridine Dyes; Arsenic and Arsenic Compounds; Arsphenamines; Copper; Gold and Gold Compounds; Iodine and Iodine Compounds; Penicillin; Sulfonamides; etc.
medicamentosa and erythema multiforme bullosum [sulfonamide compounds], 852
medicamentosa; case for diagnosis, 414
medicamentosa or psoriasis, 412
Multiformis: See Dermatitis herpetiformis
Occupational: See under Industrial Diseases
papillaris capillitii better term than "folliculitis keloidalis," *112
Poison Oak: See Rhus
psychosomatic factors in dermatoses; critical analysis of diagnostic methods of approach, *601
Radiodermatitis: See under Roentgen Rays
rat mite, 138
Rhus: See Rhus
Seborrheic: See Seborrhea
Solar: See under Light
sulfonamide psoriasiform, *525
venenata, 416
venenata; acarodermatitis urticarioides, *621
venenata due to Ace Adherent, 400
venenata due to penicillin-containing ointment, 582
venenata from atabrine, 550
venenata from contact with varnish of Japanese rifles, *110
venenata from glass fabrics, *258
venenata; lupus erythematosus or chloasma, 426
venenata; melanosis of Riehl, 148
venenata of hands, 276
venenata or dermatophytosis (eczematized), 707
venenata or erythroplasia, 845
venenata; pigmentation following application of iron salts; report of case in which it was not permanent, *692
venenata; prevention and treatment of skin diseases during war, *455
venenata; sensitization to edible mushrooms, 703
venenata; studies on poison ivy and other dermatitis producing plant parts wherein active, resinous principles are suspended in aqueous solution, 399
venenata; topical use of penicillin in treatment of pyoderma, *630
Verrucosa: See Mycosis, cutaneous
Dermatofibroma (fibrosarcoma?), 593
Dermatology; relation of dermatology and venereology, *452
military, experiences in; their interpretation in plans for improved general medical care, *441
military personnel in, *446
Navy's postgraduate education, *459
Dermatomyositis, 719
and malignant tumor, 838
case for diagnosis, 570
Dermatophytes: See Fungi
Dermatophytids: See Mycosis, cutaneous
Dermatophytosis: See Mycosis, cutaneous; Ringworm
Dermatoses: See Dermatitis; Eczema; Skin, diseases; etc.
Diabetes Mellitus; necrobiosis lipoidica diabeticorum, 427, 428
Diathesis, Allergic: See Food, allergy
Dichlormapharsen: See Syphilis
Dichlorodiphenyltrichloroethane (DDT): See Pediculosis; Scabies; etc.
Dichlorophenarsine Hydrochloride: See Syphilis
Diet and Dietetics: See also Food; Vitamins
role of food allergy in eczematoid dermatitis, *493
Dimethyl-Disulfanilamide: See Sulfonamides
Diphtheria, cutaneous, 837
cutaneous, and tropical ulcers, *360
cutaneous, occurring during war, *454
cutis or ulcers, acute pyogenic, factitial or anaerobic, 301
Disinfection and Disinfectants; self disinfection of skin; short review and some original observations, 552
Dobes, W. L.: Granulomatous Hodgkin's disease of skin with extreme eosinophilia (eosinophilic granuloma of skin?), *212
Dogs: See Rocky Mountain Spotted Fever
Dolce, F. A.: Treatment of mycotic infections by inhibiting respiration of dermatophytes, *379
Donovan Organisms: See Granuloma inguinale
Dostrovsky, A.: Progressive scleroderma of skin with cystic sclerodermal changes of lungs, *1
Dowdy, K. H.: Lichenoid dermatitis (New Guinea type), 576
Downing, J. G.: Multiple idiopathic hemorrhagic sarcoma or hemangioendotheliobiastoma, 410
Syphilitic glossitis; case for diagnosis, 407
Xanthoma disseminatum, 406
Xanthoma disseminatum (also tuberosum et planum), 405
Drant, P.: Keratosis palmaris et plantaris (epidermodysplasia verruciformis?), 856
Lupus erythematosus, 857
Drawings; leukoderma acquisitum centrifugum (Sutton) and reproduction of presentation of similar cutaneous changes on panel of altar of Isenheim, 266
Driver, J. H.: Dermatosis, progressive pigmentary, 297
Erythema chronicum migrans, 277
Larva migrans, 296
Myoblastoma, 297
Parapsoriasis, 278
Parapsoriasis en plaque, 279
Urticaria pigmentosa (nodular type), 280
Drugs, Eruptions: See also under names of drugs, as Acridine Dyes; Arsenic and Arsenic Compounds; Arsphenamines; Gold and Gold Compounds; Penicillin; Sulfonamides; etc. and under names of diseases, as Tuberculosis; etc.
stomatitis due to ingested medication; case for diagnosis, 126
Ductless Glands: See Endocrine Glands
Duhring's Disease: See Dermatitis herpetiformis
Durand-Nicholas-Favre's Disease: See Lymphogranuloma Venereum
Dwarfism: See Achondroplasia
Dyes: See Stains and Staining
Dyskeratosis: See Keratosis
Dyspnea; generalized, progressive scleroderma associated with changes in lungs, larynx and esophagus, 269
Dystrophy: See Hair; Nails

Ear, Pseudomonas aeruginosa infection treated with streptomycin, *257
squamous cell epithelioma of, 713
Ebert, M. H.: Pemphigus; case for diagnosis, 142
Pityriasis rubra pilaris with exfoliation, 141
Xanthoma eruptivum, 556
Ecthyma; topical treatment with penicillin ointment, *52
Eczema, Atopic: See Neurodermatitis
contact dermatitis of hands, 276
dermatophytosis (eczematized), 707
exudative discoid and lichenoid chronic dermatosis, 273
infantile hospital morbidity and mortality, 461
Kaposi's varicelliform eruption, *327
lichen planus-eczematoid dermatitis complex of Southwest Pacific, 549
lichenoid dermatitis, 835
nummular, 586
or carcinoma simplex of nipple, 711
role of food allergy in eczematoid dermatitis, *493
skin sensitivity due to atabrine, 550
use of histamine antagonist, beta-dimethylaminethyl benzhydryl ether hydrochloride, in allergic disease, 832

Edema: See also Elephantiasis; and under names of organs and regions, as Eyelids; etc.
angioneurotic, 591
angioneurotic; allergic reaction following typhus fever vaccine and yellow fever vaccine due to egg yolk sensitivity, 400
chronic lymphedema of eyelids, 709
giant urticaria with lymphedema, 416
Education; Navy's postgraduate education in dermatology, *459
Eggs; allergic reaction following typhus fever vaccine and yellow fever vaccine due to egg yolk sensitivity, 400
Elbow; juxta-articular nodes, origin undetermined, 129
Electricity; effect of electrical stimulation on circulation and recovery of denervated muscle, 404
Elephantiasis neuromatosa; manifestation of von Recklinghausen's disease, *233
nostras or angioneurotic edema, 591
Emotions; heat and emotional urticaria, 566
Encephalitis due to salvarsan; pathogenesis, 264
Endocrine Glands; acanthosis nigricans juvenilis associated with obesity; report of case with observations on endocrine dysfunction in benign acanthosis nigricans, *749
Endocrine Therapy: See under names of glands and hormones, as Adrenal Preparations; Pituitary Body
Eosinophils; eosinophilic granuloma of bone with cutaneous manifestations; report of case, *810
eosinophilic granuloma of skin; its relation to erythema elevatum diutinum and eosinophilic granuloma of bone; report of case, *194
eosinophilic granuloma; theoretic and practical considerations based on study of case, *176
granulomatous Hodgkin's disease of skin with extreme eosinophilia (eosinophilic granuloma of skin?), *212
pemphigus vulgaris; study of blood picture, *772
Epidermis: See Skin
Epidermodysplasia Verruciformis: See Verruca
Epidermolysis bullosa, 728
bullosa (acquired), 729
bullosa; case for diagnosis, 298
bullosa of newborn, *369
bullosa; recently described variant, *91
Epidermomycosis; Epidermophytosis: See Mycosis, cutaneous
Epidermophyton: See Fungi; Mycosis, cutaneous
Epinephrine: See Adrenal Preparations
Epithelioma, basal cell, in psoriatic patch, *375
basal cell, of forearm, 425
basal cell, or sarcoid, 734
basal squamous cell, associated with leukemia, *507
Hodgkin's disease complicated by squamous cell epithelioma of neck, 574
in lupus vulgaris (presented for therapeutic suggestions), 124
morphea-like and basal cell epithelioma of face cured by roentgen ray therapy, 585
multiple superficial epitheliomatous, 134
or kerions, 572
psoriasis; arsenical pigmentation and keratoses; squamous cell epithelioma of finger with metastasis to axillary lymph nodes, 294
squamous cell; case for diagnosis, 152
squamous cell, of ear, 713
squamous cell, with lupus vulgaris, 132
superficial basal cell, on psoriasis, 125
superficial, Bowen's disease, roentgen ray dermatitis or neurodermatitis, 851
superficial, of Bowenoid type, 287
trichoepithelioma, 726
Epstein, N. N.: Epidermolysis bullosa, 728
Monocytic leukemia; case for diagnosis, 579
Eruptions: See under Drugs, eruptions; Skin, diseases; etc.
Erythema annulare centrifugum, 582
annulare rheumaticum; skin lesions of rheumatic fever, 262
chronicum migrans, 277
elevatum diutinum, 710
elevatum diutinum; eosinophilic granuloma of skin; its relation to erythema elevatum diutinum and eosinophilic granuloma of bone; report of case, *194
induratum (Bazin), 560
multiforme bullosum and dermatitis medicamentosa [sulfonamide compounds], 852
multiforme bullosum (due to sulfonamide medication), 853
multiforme; Stevens-Johnson syndrome (eruptive fever with stomatitis and conjunctivitis), 832
palmar; its relationship to protein deficiency, 398
perstans, 846
Erythroblastosis; hemolytic disease and congenital syphilis in siblings, 263
Erythrocytes: See also Anemia; Polycythemia; etc.
pemphigus vulgaris; study of blood picture, *772
Erythroderma Exfoliativum: See Dermatitis exfoliative
Ichthyosiform: See Ichthyosis
Maculopapular: See Parapsoriasis
Erythroplasia of Queyrat: See Penis
Esophagus; generalized, progressive scleroderma associated with changes in lungs, larynx and esophagus, 269
Esposito, A. C.: Acute syphilitic bilateral total ophthalmoplegia, *686
Estrogens; atrophoderma hypoestrogenicum, 148
Ethyl Carbamates; effect of urea, urethane and other carbamates on bacterial growth, 119
Extremities: See also Foot; Legs
Blood Supply: See Raynaud's Disease; Thromboangiitis obliterans; etc.
circulation in skin of proximal parts of limbs, 404
Ulcers: See Ulcers; Varicose Veins
Eyelids, chronic lymphedema of, 709
lichen planus annularis limited to, 128
marginal blepharitis treated with penicillin; report of 48 cases, 402
skin sensitivity due to atabrine, 550
treatment of burns of face with grenz rays, 555
xanthomatous biliary cirrhosis with flat xanthomas of, 556
Eyes: See also under names of special structures and diseases of eye, as Glaucoma; etc.
ocular leprosy in Panama, 549
ocular pemphigus with scarring of skin and mucous membranes, *37
onchocerciasis, 398
paralysis; acute syphilitic bilateral total ophthalmoplegia, *686

Face, burns; treatment with grenz rays, 555
dermatophytosis caused by Trichophyton camerounense, *337
hemiatrophy, 135
leishmaniasis verrucosa of, *358
lupus erythematosus of; calcified sebaceous cysts, 860
nodular lesions; case for diagnosis, 842
Factories: See Industrial Diseases
Fakieh Grass: See under Grass
Fanning, J. L.: Roentgen ray dermatitis treated with radon ointment, 581
Fat: See also Lipoids
sclerema adiposum neonatorum of both internal and external adipose tissue, 399
Favosa: See Favus
Favre-Nicolas' Disease: See Lymphogranuloma Venereum
Favus, 404
Feet: See Foot
Fein, G.: Agranulocytosis; report of 12 cases in which it followed intensive arsenotherapy for syphilis, *57
Feldman, W. H.: Treatment of various types of cutaneous tuberculosis with promizole and streptomycin; preliminary report, *222

Felsher, M. L.: Nevus epitheliomatocylindromatosus (?), 133
Felsher, Z.: Calcinosis, generalized, 141
Disseminated subacute lupus erythematosus (?), 565
Lipoid proteinosis, 127
Fendt-Spiegler Sarcoid: See Sarcoidosis
Fever: See Malaria; Typhoid; Typhus; etc.
Rocky Mountain Spotted: See Rocky Mountain Spotted Fever
San Joaquin: See Coccidioidomycosis
Fiber Glass: See Dermatitis venenata
Fibrosarcoma or dermatofibroma, 593
Fifth Venereal Disease: See Granuloma inguinale
Fingers and Toes: See also Foot; Hand
Bowen's disease (with rare localization between second and third left toe), 266
circulation in denervated digits, 402
Nails: See Nails
pathologic findings in case of ainhum; comparison of epidermal and vascular lesions with normal toe, 261
psoriasis; arsenical pigmentation and keratoses; squamous cell epithelioma of finger with metastasis to axillary lymph nodes, 294
tumor of tactile end organs, 834
Finnerud, C. W.: Lichen planus annularis (limited to eyelids), 128
Finsen Treatment: See Lupus vulgaris
Fisher, S.: Agranulocytosis; report of 12 cases in which it followed intensive arsenotherapy for syphilis, *57
Fleas; desensitization to insect bites, 700
Flocculation Tests: See Antigens and Antibodies; Syphilis, serodiagnosis
Flood, J. M.: Role of food allergy in eczematoid dermatitis, *493
Fluorescence; unexplained phenomenon, 564
use of Purple X bulb in diagnosis of fungous diseases of scalp, *396
Foerster, H. R.: Melanodermatitis (occupational), 562
Foerster, O. H.: Melanodermatitis (occupational), 562
Folliculitis keloidalis better term than "dermatitis papillaris capillitii," *112
Food: See also Diet and Dietetics; Vitamins
anaphylactic shock from skin testing; 2 cases, 1 fatal, 400
Allergy: See also under Anaphylaxis and Allergy; and under names of various foods
allergy, role in eczematoid dermatitis, *493
Foot: See also Ankle; Fingers and Toes; etc.
dermatophytosis of hands and feet; tinea corporis (glabrosa), 848
fungous infections; comparative evaluation of preparations for prophylaxis and treatment, 838
perforating ulcer in 2 sisters, 430
Fourth Venereal Disease: See Lymphogranuloma Venereum
Fowlpox; search for virus-inactivating substances among microorganisms, 119
Fox, H.: "Folliculitis keloidalis" better term than "dermatitis papillaris capillitii," *112
Generalized, progressive scleroderma associated with changes in lungs, larynx and esophagus, 269
resignation as Chief Editor, 696
Fractures: See under Cranium; etc.
Frambesia; frambesiform tertiary syphilis, 840
Frank, L.: von Recklinghausen's disease traced through 5 generations, *109
Franks, A. G.: Basal cell epithelioma in psoriatic patch, *375
Freeman, H. E.: Necrobiosis lipoidica diabeticorum, 427
Superficial basal cell epitheliomas on psoriasis, 125
Frei Reaction: See Lymphogranuloma Venereum
Friend, F.: Topical penicillin therapy; principles of local therapy with penicillin ointment mixtures, *793
Fromer, S.: Reactions in treatment of syphilis with penicillin, *385
Fruchtbaum, L. M.: Pemphigus vulgaris, 720
Fuadin: See Creeping Eruption
Fungi: See also Actinomycosis; Blastomycosis; Moniliasis; Mycosis; Ringworm; Trichophytosis; etc.
antibacterial and fungistatic properties of propamidine, 550
comparative evaluation of preparations for prophylaxis and treatment of fungous infections of feet, 838
prevention and treatment of skin diseases during war, *455
psoriasis or onychomycosis, 850
search for virus-inactivating substances among microorganisms [Trichoderma], 119
treatment of mycotic infections by inhibiting respiration of dermatophytes, *379
use of Purple X bulb in diagnosis of fungous diseases of scalp, *396
Fungicides: See under Fungi
Furunculosis; treatment [vaccine therapy and sulfonamides], 554

Galex; contact dermatitis due to Ace Adherent, 400
Garb, J.: Dyskeratosis congenita with pigmentation, dystrophia unguium and leukoplakia oris; patient with evidence suggestive of Addison's disease, *242
Gauvain, E. A.: Creeping eruption (larva migrans?), 723
Pityriasis lichenoides chronica [Juliusberg]; case for diagnosis, 722
Genatios, T.: Pinta, 288
Superficial epithelioma of Bowenoid type, 287
Genitals: See also under names of genitals, as Penis; Vagina; etc.
angiomatoid formations in genital organs with and without tumor formation, 834
relapsing syphilids of; persistence of lesions 7 months after serologic reversion, *650
German Measles: See Rubella
Gilchrist's Disease: See Blastomycosis
Glands: See under names of glands, as Adrenals; Endocrine Glands; Lymph Nodes; etc.
Glandular Fever: See Mononucleosis, Infectious
Glaucoma, congenital, following maternal rubella, 549
Glazebrook, A. J.: Ichthyosiform changes of skin associated with internal diseases, *28
Globulin; identification of inhibitory factor of reticuloendothelial immune serum (REIS) in globulin fraction, 261
Glossitis: See Tongue
Goeckerman, W. H.: Pemphigus foliaceus; patient treated with unusual amount of acetarsone, *691
Gold and Gold Compounds; dermatitis medicamentosa due to gold sodium thiosulfate, 147
Goldbloom, A. A.: Dermatologic problems in staging area station hospital, *322
Goldman, L.: Topical penicillin therapy; principles of local therapy with penicillin ointment mixtures, *793
Goldsmith, N. R.: Possible benefit from protein hydrolysates for exfoliative dermatitis, *397
Goldstein, L.: Dermatitis herpetiformis caused by stasis dermatitis, 596
Hodgkin's disease of skin without demonstrable systemic involvement, 594
Gonorrhea: See also Venereal Diseases
keratodermia blennorrhagicum (gonorrheal dermatitis), 262
Gottron's Disease: See Ichthyosis
Gottschalk, H. R.: Lichen sclerosus et atrophicus with bullous lesions and extensive involvement; report of case, *433
Grace, A. W.: Pemphigus vulgaris; study of blood picture, *772
Graham, T. N.: Bowen's disease or tuberculosis cutis, 418
Carotenemia, 708
Periadenitis mucosa necrotica recurrens or aphthous stomatitis, 709
Grain Itch; acarodermatitis urticarioides, *621
Granulocytopenia: See Agranulocytosis

Granuloma annulare, 850, 854
annulare, generalized, 583
annulare; pseudoxanthoma elasticum, 285
annulare, sarcoid or psoriasis, 151
eosinophilic, of bone with cutaneous manifestations; report of case, *810
eosinophilic, of skin, *155
eosinophilic, of skin; its relation to erythema elevatum diutinum and eosinophilic granuloma of bone; report of case, *194
eosinophilic; theoretic and practical considerations based on study of case, *176
Fungoides: See Mycosis fungoides
granulomatous Hodgkin's disease of skin with extreme eosinophilia (eosinophilic granuloma of skin?), *212
Inguinale, 840. See also Lymphogranuloma Venereum
inguinale involving buttock and lymph node; cultivation of Donovan body in embryonic yolk, *342
inguinale or syphilitic keratosis, 578
inguinale; report of treatment of 7 cases of granuloma venereum with penicillin, 553
Lipoid: See Xanthoma
Malignant: See Hodgkin's Disease
melanotic nevus of cheek, apparently undergoing malignant degeneration, due to large underlying foreign body granuloma which has developed around bone formation, 265
new type of granulomatosis with generalized tumors simulating mycosis fungoides with fatal outcome, 265
Paracoccidioidal: See Blastomycosis
Tropicum: See Frambesia
Venereal: See Granuloma inguinale; Lymphogranuloma Venereum
Grass; acarodermatitis urticarioides (due to *Fahlek* grass), *621
Graves, J. M.: Multiple keloids, 732
Gray, M. B.: Epidermolysis bullosa; recently described variant, *91
Green, R. E.: Heat and emotional urticaria, 566
Greenbaum, S. S.: Lupus vulgaris; case for diagnosis, 304
Primary lichen amyloidosis; report of necropsy, *251
Grenz Rays: See Burns
Gross, E. R.: Calcified sebaceous cysts; lupus erythematosus of face, 860
Disseminated lupus erythematosus treated with sodium bismuth triglycollamate, 863
Disseminated lupus erythematosus treated with sodium bismuth triglycollamate ("bistrimate tablets"), 862
Keratotic lupus erythematosus treated with sodium bismuth triglycollamate ("bistrimate tablets"), 863
Larva migrans, 856
Topical treatment with penicillin ointment, *52
Guequierre, J. P.: Pachyonychia congenita; report of 2 cases with studies on therapy, *819
Gumma: See Lips; Nose; Syphilis, tertiary; Testes
Guns; dermatitis from contact with varnish of Japanese rifles, *110

Hair, abnormalities; pili torti, 703
Diseases: See Alopecia
Follicles: See Folliculitis; Keratosis follicularis
new type of familial and hereditary agenesis and dystrophy of, 267
Plucking: See Trichotillomania
trichofolliculoma, 267
Hall, A. F.: Epithelioma in lupus vulgaris (presented for therapeutic suggestions), 124
Halpert, B.: Epidermolysis bullosa of newborn, *369
Hand: See also Fingers and Toes
calcified sebaceous cysts; lupus erythematosus of face, 860
dermatophytosis of hands and feet; tinea corporis (glabrosa), 848
hyperkeratosis penetrans; report of case of probable variant of Kyrle's disease, *633
Hanfling, S. L.: Dermatologic problems in staging area station hospital, *322
Hansen's Disease: See Leprosy
Hay Fever: See Anaphylaxis and Allergy
Hazen, H. H.: Mycosis fungoides and similar conditions in Negro, *111
Heat and emotional urticaria, 566
Heid, B.: Epidermolysis bullosa; case for diagnosis, 298
Lichen planus with involvement of palms, 295
Lymphoblastoma; case for diagnosis, 293
Psoriasis; arsenical pigmentation and keratosis; squamous cell epithelioma of finger with metastasis to axillary lymph nodes, 294
Helms, R. W.: Congenital absence of valves in veins as cause of varicosities, *639
Helwig, E. B.: Granuloma inguinale involving buttock and lymph node; cultivation of Donovan Body in embryonic yolk, *342
Hemangioendothelioblastoma or multiple idiopathic hemorrhagic sarcoma, 410
Hemangioma: See also Angioma
cavernous, of lip, 145
Hemiatrophy: See Face
Hemophilus Ducreyi: See Chancroid
Hemopoietic System, Diseases: See Anemia; Leukemia; etc.
Hemorrhage, Cutaneous: See Purpura
Hepar Lobatum: See Liver
Hepatitis: See Jaundice; Liver
Heredity: See Neurofibromatosis
Herpes gestationis, 715
simplex; Kaposi's varicelliform eruption, *327
zoster and chickenpox, 263
zoster in isolated community, 701
zoster; varicella herpetiformis, 839
Herxheimer Reaction: See Neurosyphilis
Herzberg's Stain: See Stains and Staining
Hidradenitis: See under Sweat Glands
Hill, W. R., Jr.: Sarcoidosis of skin, 711
Syphilis of skin (primary, recurrent), 718
Hinshaw, H. C.: Treatment of various types of cutaneous tuberculosis with promizole and streptomycin; preliminary report, *222
Histamine: See Anaphylaxis and Allergy; Dermatitis; Eczema; Urticaria
Hitch, J. M.: Systemic treatment of creeping eruption, *664
Hodgkin's Disease complicated by squamous cell epithelioma of neck, 574
cutaneous torulosis in patient with, 738
granulomatous, of skin with extreme eosinophilia (eosinophilic granuloma of skin?), *212
mycosis fungoides and similar conditions in Negro, *111
of skin without demonstrable systemic involvement, 594
Hoffman, B. J.: Topical use of penicillin in treatment of pyoderma, *630
Holley, H. L.: Agranulocytosis; report of 12 cases in which it followed intensive arsenotherapy for syphilis, *57
Holman, J. C., Jr.: Use of trichophytin in thromboangiitis obliterans, *512
Hormones: See Adrenal Preparations; Androgens; Endocrine Glands; Estrogens; etc.
Hospitals; administrative problems in military dermatology, *448
dermatologic problems in staging area station hospital, *322
morbidity and mortality of infantile eczema, 401
Hubler, W. R.: Lichen sclerosus et atrophicus; case for diagnosis, 284
Papulopustular verrucous sporotrichosis simulating blastomycosis, 290
Pseudoxanthoma elasticum, 285
Reticuloendotheliosis or mycosis fungoides, 286
Hunt Syndrome: See Herpes zoster
Hydroa vacciniforme (hydroa aestivale), 419
Hydrogen peroxide, glycerite of; effects on infections of skin and mucous membranes, *801
Hyman, A. B.: Epidermolysis bullosa; recently described variant, *91
Hyperergy: See Anaphylaxis and Allergy
Hyperkeratosis: See Keratosis
Hypoparathyroidism: See under Parathyroid
Hypophysis: See Pituitary Body
Hypotrichosis: See Alopecia

Ichthyosis and juvenile acanthosis nigricans, 411
hystrix or psoriasis, 268
ichthyosiform changes of skin associated with internal diseases, *28
Icterus: See Jaundice
Idiosyncrasy: See Anaphylaxis and Allergy; Drugs; and under names of substances; etc.
Immunity: See Anaphylaxis and Allergy; Lymphogranuloma Venereum; Serum; etc.
Impetigo contagiosa; topical treatment with penicillin ointment, *52
Industrial Diseases; melanodermatitis (occupational), 562
melanosis of Riehl, 148
Infants: See also Children
Addison's disease in, 835
alopecia areata in, 143
desensitization to insect bites, 700
hospital morbidity and mortality of infantile eczema, 401
newborn; epidermolysis bullosa of, *369
newborn; sclerema adiposum neonatorum of both internal and external adipose tissue, 399
Infection: See under Skin; Wounds
Infectious Diseases: See Gonorrhea; Syphilis; Typhoid; etc.
Inguinal Glands: See Lymph Nodes
Injections: See also Sodium chloride; Typhoid; etc.
intramuscular; penicillin in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin in single and multiple doses in isotonic solution of sodium chloride and peanut oil-beeswax by intramuscular injection, *741
Inoculation: See under names of diseases, as Furunculosis; Syphilis; Typhoid; Yellow Fever; Verruca; etc.
Insects, bites; benadryl in dermatologic therapy, *101
bites, desensitization to, 700
Instruments: See Apparatus
Internal Secretions: See Endocrine Glands
Intestines; unilateral ulceration of mouth (tuberculosis orificialis?), probably with miliary and ileocecal involvement, 580
Iodides: See Iodine and Iodine Compounds
Iodine and Iodine Compounds; iodide dermatitis, 305
Ion Transfer; treatment of epidermophytosis on extremities with iontophoresis of copper, 122
Iontophoresis: See Ion Transfer
Iron salts, pigmentation following application of; report of case in which it was not permanent, *692
Itching: See Pruritus
Ivy Poisoning: See under Rhus

Jacobi-Petges' Disease: See Poikiloderma atrophicans vasculare
Jadassohn's Disease: See Atrophy
Japan and Japanese; dermatitis from contact with varnish of Japanese rifles, *110
Jaundice: See also Liver
falsely positive Wassermann and Kahn reactions in infective hepatitis, 701
Jennison, D. B.: Granuloma inguinale involving buttock and lymph node; cultivation of Donovan body in embryonic yolk, *342
Jensen, A. K.: Porokeratosis (Mibelli), 127
Jericho Boil: See Leishmaniasis
Johnson-Stevens Syndrome: See Erythema multiforme
Joints: See under names of joints
Diseases: See Arthritis; etc.
Jordon, J. W.: Clinical use of new antihistaminic compound (pyribenzamine) in certain cutaneous disorders, *309
Jungle Sores: See Ulcers, tropical
Jungle Warfare: See Military Medicine
Juxta-Articular Nodes: See Nodes

Kagen, E.: Lupus vulgaris with squamous cell epithelioma, 132
Kagen, M. S.: Acute disseminated lupus erythematosus, 136
Case for diagnosis, 570
Dermatomyositis; case for diagnosis, 570
Lymphoblastoma; case for diagnosis, 142
Kagen, M. S.—Continued
Pellagra, 570
Pemphigus; case for diagnosis, 142
Pityriasis rubra pilaris with exfoliation, 141
Scrofuloderma, 132
Subacute disseminated lupus erythematosus, 136
Xanthoma eruptivum, 556
Kahn Test: See also under Syphilis
falsely positive Wassermann and Kahn reactions in infective hepatitis, 701
Kala-Azar: See Leishmaniasis
Kanee, B.: Ocular pemphigus with scarring of skin and mucous membranes, *37
Kanof, A.: Undecylenic and propionic acids in prevention and treatment of dermatophytosis, *391
Kaposi's Sarcoma: See Sarcoma
Varicelliform Eruption: See Pyoderma
Kats, S.: Annular, macular syphilid, 300
Dermatofibroma (flurosarcoma?), 593
Iodide dermatitis, 305
Katzenellenbogen, I.: Acarodermatitis urticarioides, *621
Kaufman, W. H.: Treatment of early acquired syphilis with 600,000 units of sodium penicillin, *644
Keddie, F. M.: Keratosis follicularis (Darier's disease), 730
Kelly, R. J.: Dermatitis herpetiformis; case for diagnosis, 150
Keloid, 300. See also Cicatrix
multiple, 732
multiple, in twin sisters, 426
Kendall, R. F.: Undecylenic acid in treatment of monilial vulvovaginitis, *113
Keratoderma: See Keratosis
Keratosis: See also Ichthyosis
acrokeratosis verruciformis (Hopf), 598
and arsenical pigmentation; psoriasis; squamous cell epithelioma of finger with metastasis to axillary lymph nodes, 294
Bowen's disease or tuberculosis cutis, 418
bullous dyskeratosis (familial benign chronic pemphigus), 730
dyskeratosis congenita with pigmentation, dystrophia unguium and leukoplakia oris; patient with evidence suggestive of Addison's disease, *242
follicularis (Darier's disease), 730
follicularis; epidermolysis bullosa; recently described variant, *91
hyperkeratosis of palms and soles due to ingestion of quinacrine hydrochloride, *256
hyperkeratosis penetrans; report of case of probable variant of Kyrle's disease, *633
keratodermia blennorrhagicum (gonorrheal dermatitis), 262
keratotic lupus erythematosus treated with sodium bismuth triglycollamate ("bistrimate tablets"), 863
pachyonychia congenita; report of 2 cases with studies on therapy, *819
palmaris et plantaris (epidermodysplasia verruciformis?), 856
parakeratosis variegata (parapsoriasis variegata S. reticularis), 704
pilaris; case for diagnosis, 138
pityriasis rubra pilaris with exfoliation, 141
porokeratosis (Mibelli), 127
syphilitic, 578
Kerion: See Trichophytosis
Kline, B. S.: Cardiolipin-lecithin antigen; recent development toward single standard test of blood for syphilis, *514
Knowles, F. C.: Actinomycosis, 299
Malignant melanoma, 302
Ulcers; acute pyogenic, factitial or anaerobic, 301
Kolmer, J. A.: Penicillin in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin in single and multiple doses in isotonic solution of sodium chloride and peanut oil-beeswax by intramuscular injection, *741
Kolodny, M. H.: Cutaneous diphtheria and tropical ulcers, *360
Konheim, W.: Basal squamous cell epithelioma associated with leukemia, *507
Koretsky, L.: Eczema or carcinoma simplex of nipple, 711

Krysa, H.: Facial hemiatrophy, 135
Linear scleroderma with spina bifida, 130
Xanthomatous biliary cirrhosis with flat xanthomas of eyelids, 556
Kyrle's Disease: See Keratosis

Lacrimal Organs; dacryocystitis and dermatitis seborrheica, 717
Laennec's Disease: See under Liver, cirrhosis
Lafreniere, E. A.: Mycosis fungoides, 718
Lamb, J. H.: Epidermolysis bullosa of newborn, *369
Lane, C. G.: Dermatomyositis, 719
Herpes gestationis, 715
Pyoderma gangrenosum, 714
Squamous cell epithelioma of ear, 713
LaRosa, W. V.: Lipoidosis cutis et mucosae: report of case, *42
Larva Migrans: See Creeping Eruption
Larynx; generalized, progressive scleroderma associated with changes in lungs, larynx and esophagus, 269
search for virus-inactivating substances among microorganisms, 119
Laymon, C. W.: Acanthosis nigricans (juvenile type), 144
Cutis verticis gyrata, 146
Kerions, 572
Leather; dermatophytosis (eczematized) or dermatitis venenata [from shoe leather], 707
Lecithin: See Lipoids
Legs: See also Extremities; Foot
purpuric eruption of lower extremities resembling Schamberg's disease; case for diagnosis, 148
Ulcers: See Ulcers; Varicose Veins
Leishmaniasis; leishmania vaccine test in leishmaniasis of skin (oriental sore); quantitative experiments, *658
verrucosa of face, *358
Lentz, J. W.: Lichen planus (lichen ruber moniliformis?), 858
Pustular syphilis, 859
Leprosy; modes of transmission of Hansen's disease, 702
nerve lesions of, *783
neural; case for diagnosis, 569
ocular, in Panama, 549
or sarcoid, 589
palm oil in, 702
tuberculoid, of lupoid appearance, *474
visit to leper colony, 702
Lerner, M.: Pemphigus erythematosus (Senear-Usher type), 721
Leukemia associated with basal squamous cell epithelioma, *507
chloroma; clinicopathologic study of 2 cases, 398
chronic myeloid, or epidermodysplasia verruciformis, 280
human; attempted transmission in man, 551
leukemid or scabies, 595
monocytic; case for diagnosis, 579
mycosis fungoides and similar conditions in Negro, *111
Leukemid: See Leukemia
Leukocytes: See Eosinophils; Leukemia; Mononucleosis, Infectious; etc.
Leukoderma: See Vitiligo
Leukopenia: See Granulocytopenia
Leukoplakia: See Mouth
Lever, W. F.: Dermatitis seborrheica, 717
Eosinophilic granuloma of skin; its relation to erythema elevatum diutinum and eosinophilic granuloma of bone; report of case, *194
Hidradenitis suppurativa, 713
Levine, B.: Acanthosis nigricans, 291
Lewis, G. M.: Dermatophytosis (eczematized), 707
Eosinophilic granuloma; theoretic and practical considerations based on study of case, *176
Lice: See Pediculosis
Lichen Amyloidosis: See Amyloidosis
Atrophicus: See Lichen planus
corneus hypertrophicus; unusual dermatosis simulating lichen planus and lichen corneus hypertrophicus; report of 6 cases, *12
Lichen—Continued
lichenoid dermatitis, 835
lichenoid dermatitis (New Guinea type), 576
nitidus, 567
planopilaris; case for diagnosis, 131
planus, 153
planus annularis; case for diagnosis, 131
planus annularis limited to eyelids, 128
planus atrophicus or linear nevus, 268
planus-eczematoid dermatitis complex of Southwest Pacific, 549
planus (lichen ruber moniliformis?), 858
planus, linear, 724
planus, lupus erythematosus or pemphigus, 270
planus tropicalis, atypical, *535
planus; unusual dermatosis simulating lichen planus and lichen corneus hypertrophicus; report of 6 cases, *12
planus with involvement of palms, 295
ruber moniliformis; morbus moniliformis lichenoides; variant types, *674
ruber moniliformis or lichen planus, 858
sclerosis et atrophicus, 149, 284
sclerosis et atrophicus with bullous lesions and extensive involvement; report of case, *433
Tropicus: See Miliaria
Urticatus: See Urticaria, papular
Lichenification: See Neurodermatitis; Prurigo nodularis
Lichens: See Fungi
Lieberthal, E. P.: Nevus epitheliomatocylindromatosus (?), 133
Light; birefringence in tissues, 834
hydroa vacciniforme (hydroa aestivale), 419
lupus erythematosus [sensitivity to sunlight], 857
protective skin coatings for prevention of sunburn, 118
studies in hypersensitivity to, 836
urticaria solare (4000-5000A), 836
Limbs: See Extremities; Legs
Lingua: See Tongue
Lipid Proteinosis: See Lipoids, metabolism
Lipids: See Lipoids
Lipoidosis: See Lipoids
Lipoids: See also Fat
cadiolipin-lecithin antigen; recent development toward single standard test of blood for syphilis, *514
lipoidosis cutis et mucosae; report of case, *42
metabolism; lipid proteinosis, 127
xanthoma disseminatum, 406
xanthoma disseminatum and tuberosum et planum, 405
Lips; angioneurotic edema, 591
cancer, radium treatment of, 839
cavernous hemangioma of, 145
gumma of nose and upper lip, 145
Liver, cirrhosis; xanthomatous biliary cirrhosis with flat xanthomas of eyelids, 556
function; clinical and laboratory studies in therapeutic malaria, 833
hepar lobatum; clinical significance of anatomic changes, 834
ichthyosiform changes of skin associated with internal diseases, *28
Livingood, C. S.: Experiences in military dermatology; their interpretation in plans for improved general medical care, *441
Loeffler's Syndrome: See Eosinophils; Lungs, pathology
Luetin Test: See under Syphilis
Lungs; generalized, progressive scleroderma associated with changes in lungs, larynx and esophagus, 269
pathology; "eosinophilic granulomas" of skin, *155
pathology; eosinophilic granuloma; theoretic and practical considerations based on study of case, *176
progressive scleroderma of skin with cystic sclerodermal changes of, *1
Tuberculosis: See Tuberculosis, pulmonary
Lupoid: See Sarcoidosis

Lupus: See also Tuberculids; Tuberculosis
annularis of cervical region simulating tertiary syphilis, 554
erythematosus, 135, 857
erythematosus, acute disseminated, 136
erythematosus, disseminated subacute (?), 565
erythematosus, disseminated, treated with sodium bismuth triglycollamate ("bistrimate tablets"), 862, 863
erythematosus, keratotic, treated with sodium bismuth triglycollamate ("bistrimate tablets"), 863
erythematosus of face; calicified sebaceous cysts, 860
erythematosus of scalp, 143
erythematosus or chloasma, 426
erythematosus or pemphigus, 270
erythematosus or Spiegler-Fendt sarcoid, 736
erythematosus, subacute disseminated, 136
Pernio: See Sarcoidosis
tuberculoid leprosy of lupoid appearance, *474
vulgaris, 149, 598
vulgaris; case for diagnosis, 304
vulgaris, epithelioma in (presented for therapeutic suggestions), 124
vulgaris, Finsen treatment and significance to rational combating of, 122
vulgaris; treatment of various types of cutaneous tuberculosis with promizole and streptomycin; preliminary report, *222
vulgaris with squamous cell epithelioma, 132
Lymph Nodes: See also Lymphosarcoma; Mononucleosis, Infectious; etc.
granuloma inguinale involving buttock and lymph node; cultivation of Donovan body in embryonic yolk, *342
periadenitis mucosa necrotica recurrens or aphthous stomatitis, 709
psoriasis; arsenical pigmentation and keratoses; squamous cell epithelioma of finger with metastasis to axillary lymph nodes, 294
relationship of Boeck's sarcoid and tuberculosis; report of case in which tuberculosis of lymph nodes was associated with features highly suggestive of sarcoid, 399
Lymphadenopathy: See Lymph Nodes
Lymphangioma circumscriptum congenitale or angioneurotic edema, 591
Lymphedema: See Edema; Elephantiasis
Lymphoblastoma, 140, 735
case for diagnosis, 142, 293
Lymphogranuloma, Benigna: See Sarcoidosis
Hodgkin's: See Hodgkin's Disease
Inguinale: See Granuloma inguinale; Lymphogranuloma Venereum
Schaumann's: See Sarcoidosis
Lymphogranuloma Venereum from immunobiologic point of view, 121
Lymphopathia Venerea: See Lymphogranuloma Venereum
Lymphosarcoma; ichthyosiform changes of skin associated with internal diseases, *28
Lynch, F. W.: Acne vulgaris treated with vitamin A, *355
Benadryl in dermatologic therapy, *101
Kaposi's varicelliform eruption, *327

McFarland, A. R.: Morbus moniliformis lichenoides; variant types, *674
Machacek, G.: Mycosis fungoides or arsenical dermatitis, 275
MacKee, G. M.: Angiopericytoma; case for diagnosis, 726
Madden, J. F.: Lichen sclerosus et atrophicus, 149
Lupus vulgaris, 149
Madura Foot: See Mycetoma
Maduromycosis: See Mycetoma
Majocchi's Disease: See Purpura annularis telangiectodes
Mal del Pinto: See Pinta
Malaria, therapeutic, clinical and laboratory studies of liver function in, 833
Malformations: See under names of diseases, organs and regions, as Atrophy; Hair, abnormalities; Nails, abnormalities; Skin, abnormalities; etc.
Mammary Gland: See Breast
Mariano, J.: Tuberculoid leprosy of lupoid appearance, *474
Materia Medica: See Drugs
May, S. B.: Necrobiosis lipoidica diabeticorum, 428
Measles, German: See Rubella
Medical Societies: See Societies
Medicine, Aviation: See Aviation and Aviators
Military: See Military Medicine
Naval: See Naval Medicine
Psychosomatic: See Mind, body and mind
Tropical: See Tropical Medicine
Meier, D. E.: Neural leprosy; case for diagnosis, 569
Meininger, W. M.: Relapse following penicillin therapy of early syphilis, 572
Syphilitic keratosis, 578
Melanin: See also Addison's Disease; Melanoma; Pigmentation
melanodermatitis (occupational), 562
melanosis of Riehl, 148
Melanoma, malignant, 302
multiple idiopathic hemorrhagic sarcoma or hemangioendothelioblastoma, 410
Melanosis: See Melanin
Meniscocytes: See Anemia, sickle cell
Mental Diseases: See Neuroses and Psychoneuroses
Metals: See Copper; etc.
Metasyphilis: See Syphilis, congenital
Methyl Testosterone: See Androgens
Mibelli's Disease: See under Keratosis
Michelson, H. E.: Kerions, 572
Melanosis of Riehl, 148
Microfilaria: See Onchocerciasis
Microscopy: See also Stains and Staining; Tissue; etc.
birefringence in tissues, 834
capillary, with reference to capillary petechiae, 832
Microsporon; tinea capitis due to Microsporon audouini (3 cases), 146
lanosum; tinea capitis in southeastern Tennessee, *258
Miliaria; prickly heat, 554
tropical anhidrotic asthenia (thermogenic anhidrosis) and its relationship to prickly heat, 260
Military Medicine: See also Aviation and Aviators; etc.
administrative problems in military dermatology, *448
atypical lichen planus tropicalis, *535
chief advances in dermatologic diagnosis and treatment occurring during war, *453
deficiencies in available methods of dermatologic therapy during war, *456
dermatitis from contact with varnish of Japanese rifles, *110
dermatologic problems in staging area station hospital, *322
experiences in military dermatology; their interpretation in plans for improved general medical care, *441
hyperkeratosis of palms and soles due to ingestion of quinacrine hydrochloride, *256
incidence of dermatologic disease in Army, *442
lichen planus-eczematoid dermatitis complex of Southwest Pacific, 549
onchocerciasis, 398
personnel in military dermatology, *446
planning and investigations to prevent and cure diseases of skin in Army, *445
psychosomatic factors in dermatoses; critical analysis of diagnostic methods of approach, *601
quinacrine hydrochloride dermatitis; case for diagnosis, 291
reactions to penicillin, 549
rehabilitation of patients suffering from skin disease, 263
relation of dermatology and venereology, *452

Military Medicine—Continued
topical use of penicillin in treatment of pyoderma, *630
unusual dermatosis simulating lichen planus and lichen corneus hypertrophicus; report of 6 cases, *12
Miller, H. E.: Bullous dyskeratosis (familial benign chronic pemphigus), 730
Idiopathic multiple pigmented sarcoma of Kaposi, 575
Mycetoma [maduromycosis]; case for diagnosis, 733
Miller, J. L.: Boeck's sarcoid, 153
Granuloma annulare, 850
Hydroa vacciniforme (hydroa aestivale), 419
Lichen planus, 153
Pityriasis rosea, 154
Psoriasis or onychomycosis, 850
Superficial epithelioma, Bowen's disease, roentgen ray dermatitis or neurodermatitis, 851
Syringocystadenoma, 420
Vascularitis of unknown origin; case for diagnosis, 849
Milstone, J. H.: Granuloma inguinale involving buttock and lymph node; cultivation of Donovan body in embryonic yolk, *342
Minadeo, A. R.: Parapsoriasis, 278
Parapsoriasis en plaque, 279
Urticaria pigmentosa (nodular type), 280
Mind, body and mind; psychosomatic factors in dermatoses; critical analysis of diagnostic methods of approach, *601
Miskjian, H. G.: Quinacrine hydrochloride dermatitis; case for diagnosis, 291
Mitchell, J. H.: Case for diagnosis, 131
Psoriasis of palms, 134
Mites; acarodermatitis urticarioides, *621
rat mite dermatitis, 138
Moeller's Glossitis: See Tongue
Molds: See Fungi
Moles: See Nevi
Molluscum contagiosum, cytology, with significance of so-called "vacuoles," 260
Moniliasis; chronic latent oral moniliasis (thrush); report of case of 12 years' duration in which disease was resistant to treatment, *85
undecylenic acid in treatment of monilial vulvovaginitis, *113
Monocytes: See Leukemia, monocytic
Mononucleosis, Infectious; analysis of 26 clinical and 340 subclinical cases, 832
Montgomery, O. F.: Epidermolysis bullosa (acquired), 729
Sarcoid or basal cell epithelioma, 734
Montgomery, R. M.: Dermatitis venenata, 416
Dermatophytosis of hands and feet; tinea corporis (glabrosa), 848
Epidermodysplasia verruciformis, 845
Erythema perstans, 846
Purpura annularis telangiectodes, 847
Squamous cell epithelioma; case for diagnosis, 152
Morbus moniliformis lichenoides; variant types, *674
Morgan, D. B.: Use of Purple X bulb in diagnosis of fungous diseases of scalp, *396
Morphea: See Scleroderma
Morrow, G.: Leiomyoma cutis, 732
Morrow-Brooke's Disease: See Keratosis follicularis
Mouth: See also Stomatitis; etc.
chronic latent oral moniliasis (thrush); report of case of 12 years' duration in which disease was resistant to treatment, *85
dyskeratosis congenita with pigmentation, dystrophia ungulum and leukoplakia oris; patient with evidence suggestive of Addison's disease, *242
lichen sclerosus et atrophicus, 149
periadenitis mucosa necrotica recurrens or aphthous stomatitis, 709
tuberculosis cutis orificialis with underlying pulmonary tuberculosis, 571
Mouth—Continued
unilateral ulceration (tuberculosis orificialis?), probably with miliary and ileocecal involvement, 580
Mucous Membrane: See also Lips; Mouth; Nose; etc.
effects of glycerite of hydrogen peroxide on infections of skin and mucous membranes, *801
epithelial symptoms caused by various deficiencies, 555
erythroplasia of glans penis (Bowen's disease of mucous membranes), 265
lichen planus, 153
lipoidosis cutis et mucosae; report of case, *42
ocular pemphigus with scarring of skin and mucous membranes, *37
periadenitis mucosa necrotica recurrens or aphthous stomatitis, 709
Murphy, W. W.: Epidermolysis bullosa; case for diagnosis, 298
Lichen planus with involvement of palms, 295
Lymphoblastoma; case for diagnosis, 293
Pinta, 288
Psoriasis; arsenical pigmentation and keratosis; squamous cell epithelioma of finger with metastasis to axillary lymph nodes, 294
Superficial epithelioma of Bowenoid type, 287
Muscles, denervated; contractility and excitability; 404
effect of electrical stimulation on circulation and recovery of denervated muscle, 404
Mushrooms: See also Fungi
edible, sensitization to, 703
Mycetoma; Madura foot; first report from Isthmus of Panama, *761
maduromycosis; case for diagnosis, 733
Mycology: See Fungi; Mycosis
Mycosis: See also Actinomycosis; Blastomycosis; Moniliasis; Mycetoma; Ringworm; Stomatitis; Tinea; etc.
cutaneous; dermatophytosis (eczematized), 707
cutaneous; dermatophytosis of hands and feet; tinea corporis (glabrosa), 848
cutaneous; treatment of epidermophytosis on extremities with iontophoresis of copper, 122
cutaneous; undecylenic and propionic acids in prevention and treatment of dermatophytosis, *391
dermatophytosis of face caused by Trichophyton camerounense, *337
eosinophilic granuloma; theoretic and practical considerations based on study of case, *176
fungoides, 271, 562, 718
fungoides and similar conditions in Negro, *111
fungoides; new type of granulomatosis with generalized tumors simulating mycosis fungoides with fatal outcome, 265
fungoides or arsenical dermatitis, 275
fungoides or Hodgkin's disease complicated by squamous cell epithelioma of neck, 574
fungoides or poikiloderma vasculare atrophicans, 706
fungoides or reticuloendotheliosis, 286
fungoides [roentgen therapy], 122
lichen planus-eczematoid dermatitis complex of Southwest Pacific, 549
treatment of mycotic infections by inhibiting respiration of dermatophytes, *379
Myoblastoma, 297
Myoma; leiomyoma cutis, 732
Myositis: See Dermatomyositis

Nails, abnormalities; longitudinal grooving of nails caused by synovial lesions, *828
abnormalities; pachyonychia congenita; report of 2 cases with studies on therapy, *819
capillary microscopy with reference to capillary petechiae, 832

Nails—Continued
dyskeratosis congenita with pigmentation, dystrophia unguium and leukoplakia oris; patient with evidence suggestive of Addison's disease, *242
psoriasis or onychomycosis, 850
Narcotics: See under names of drugs
Nares: See Nose
Naval Medicine: See also Aviation and Aviators; Hospitals; Military Medicine; etc.
dermatophytosis of hands and feet; tinea corporis (glabrosa), 848
lichenoid dermatitis (New Guinea type), 576
Navy's postgraduate education in dermatology, *459
prickly heat, 554
toxic effects of arsenical compounds as administered in United States Navy in 1944, with reference to arsenical dermatitis, 262
undecylenic and propionic acids in prevention and treatment of dermatophytosis, *391
Navies: See Naval Medicine
N.B.I.N.: See Pediculosis
Neck, Hodgkin's disease complicated by squamous cell epithelioma of, 574
Necrobiosis Lipoidica: See Skin, diseases
Necropsies: See Amyloidosis
Negroes, Diseases: See also Ainhum
diseases; mycosis fungoides and similar conditions in Negroes, *111
Nelson, L. M.: Unusual dermatosis simulating lichen planus and lichen corneus hypertrophicus; report of 6 cases, *12
Neoarsphenamine: See Arsphenamines; and under names of various diseases, as Syphilis; etc.
Neoplasms: See Cancer; Sarcoma; Tumors; etc.
Nerves: See also Neurons
circulation in denervated digits, 402
contractility and excitability of denervated muscle, 404
effect of electrical stimulation on circulation and recovery of denervated muscle, 404
epinephrine and denervation, 403
inflammation and trophic ulcers in denervated areas, 403
lesions of leprosy, *783
neural leprosy; case for diagnosis, 569
sebaceous secretion and denervation, 404
studies in denervation; methods, 402
tumor of tactile end organs, 834
Nervous System: See Brain; Nerves; etc.
Syphilis: See Neurosyphilis
Netherton, E. W.: Lichen sclerosus et atrophicus; case for diagnosis, 284
Papulopustular verrucous sporotrichosis simulating blastomycosis, 290
Pseudoxanthoma elasticum, 285
Reticuloendotheliosis or mycosis fungoides, 286
Neurodermatitis; hypertrophic or tumid type; case for diagnosis, 708
superficial epithelioma, Bowen's disease or roentgen ray dermatitis, 851
Neurofibromatosis; elephantiasis neuromatosa; manifestation of von Recklinghausen's disease, *233
von Recklinghausen's disease traced through 5 generations, *109
Neurons; mechanism of axonal vasodilation, 403
Neuroses and Psychoneuroses; psychosomatic factors in dermatoses; critical analysis of diagnostic methods of approach, *601
trichotillomania, 859
Neurosyphilis; use of penicillin in treatment of syphilis of central nervous system, 697
Neves, J. A.: Tinea nigra, *67
Nevi: See also Angioma
epithelioma tocylindromatosus (?), 133
ichthyosis hystrix or psoriasis, 268
junction, 583
juvenile acanthosis nigricans and ichthyosis, 411
linear, or lichen planus atrophicus, 268
linearis or localized scleroderma (morphea), 716
Nevi—Continued
melanotic, of cheek, apparently undergoing malignant degeneration, due to large underlying foreign body granuloma which has developed around bone formation, 265
pigmentosus, 269
Vascular: See Angioma
Newborn Infants: See Infants, newborn
Nickerson, W. J.: Treatment of mycotic infections by inhibiting respiration of dermatophytes, *379
Nicolas-Favre Disease: See Lymphogranuloma Venereum
Niedelman, M. L.: Acrokeratosis verruciformis (Hopf), 598
Cushing's adrenogenital syndrome, 855
Dermatitis herpetiformis, 854
Granuloma annulare, 854
Keloids, 300
Lupus vulgaris, 598
Pemphigus vulgaris, 592
Pustular syphilis, 859
Niederman, D. J.: Juxta-articular nodes, origin undetermined, 129
Lichen nitidus, 567
Rat mite dermatitis, 138
Nipples: See Breast
Nodes: See also Erythema nodosum; Lymph Nodes; Panniculitis; Rheumatic Fever; etc.
juxta-articular, origin undetermined, 129
Nomenclature; "eosinophilic granulomas" of skin, *155
eosinophilic granuloma; theoretic and practical considerations based on study of case, *176
epidermolysis bullosa; recently described variant, *91
"folliculitis keloidalis" better term than "dermatitis papillaris capillitii," *112
hyperkeratosis penetrans; report of case of probable variant of Kyrle's disease, *633
Kaposi's varicelliform eruption, *327
modes of transmission of Hansen's disease (leprosy), 702
quinacrine hydrochloride dermatitis occurring during war, *453
tinea nigra, *67
venospasm; its part in producing clinical picture of Raynaud's disease, 399
Nose; gumma of nose and upper lip, 145
rhinoscleroma, 733
Novy, F. G., Jr.: Rhinoscleroma, 733
Nutrition: See Diet and Dietetics; Food; Vitamins; etc.

Obermayer, M. E.: Parapsoriasis with pigmentation or urticaria pigmentosa, 429
Obesity associated with acanthosis nigricans juvenilis; report of case, with observations on endocrine dysfunction in benign acanthosis nigricans, *749

Obituaries:
Chipman, Ernest Dwight, 432, 694
Pels, Isaac R., 432
Urbach, Erich, 115, 545
Whitfield, Arthur, 432

Occupational Dermatitis: See Industrial Diseases
Oil, Peanut: See Peanut Oil
Therapy: See Syphilis
Ointments: See also under Rhus; Skin, diseases
bases; scientific principles in design and choice, 553
clinical experience with ointment of synthetic coal tar, *683
dermatitis venenata due to penicillin-containing ointment, 582
future of B. P. ointments, 401
some newer bases for use in cutaneous therapy, 260
topical penicillin therapy; principles of local therapy with penicillin ointment mixtures, *793
topical treatment with penicillin ointment, *52

O'Leary, P. A.: Treatment of various types of cutaneous tuberculosis with promizole and streptomycin; preliminary report, *222
Omens, D. V.: Acute disseminated lupus erythematosus, 136
Case for diagnosis, 570
Scrofuloderma, 132
Tuberculosis cutis orificialis with underlying pulmonary tuberculosis, 571
Omens, H. D.: Acute disseminated lupus erythematosus, 136
Case for diagnosis, 131, 570
Scrofuloderma, 132
Tuberculosis cutis orificialis with underlying pulmonary tuberculosis, 571
Onchocerciasis, 398
Onychia: See under Nails, abnormalities
Onychodystrophy: See under Nails
Onychomycosis: See Nails
Ophthalmoplegia: See Eyes, paralysis
Oppenheim, M.: Blastomycosis, 561
Oriental Sore: See Leishmaniasis
Osborne, E. D.: Clinical use of new antihistaminic compound (pyribenzamine) in certain cutaneous disorders, *309
Otsuka, M.: Tuberculosis cutis orificialis with underlying pulmonary tuberculosis, 571
Outpatient Department: See Syphilis, early
Ovary, cancer; dermatomyositis and malignant tumor, 838

Pachyonychia: See Keratosis; Nails, abnormalities
Paget's Disease: See Breast
Palm Oil, Therapy: See Leprosy
Panniculitis or erythema induratum (Bazin), 560
Parakeratosis: See Parapsoriasis
Paralysis: See Eyes, paralysis; etc.
Parapsoriasis, 278
en gouttes, 589
en plaque, 279
parakeratosis variegata (parapsoriasis variegata S. reticularis), 704
pityriasis lichenoides chronica [Juliusberg]; case for diagnosis, 722
with pigmentation or urticaria pigmentosa, 429
Parasites; parasitic infection or scabies, 597
Parathyroid; chronic idiopathic hypoparathyroidism with superimposed Addison's disease in child, 835
Pardo-Castello, V.: Nerve lesions of leprosy, *783
Parotid Gland, development of sebaceous glands from intralobular ducts of, 117
Patch Test: See Anaphylaxis and Allergy; Food, allergy
Peanut Oil; penicillin in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin in single and multiple doses in isotonic solution of sodium chloride and peanut oil-beeswax by intramuscular injection, *741
Pediatrics: See Children; Infants; etc.
Pediculoides Ventricosus: See Grain Itch
Pediculosis and scabies treated with benzyl benzoate, DDT and benzocaine emulsion, 835
combination treatment for lice and scabies, 835
Pelada: See Alopecia areata
Peladang: See Pinta
Pellagra, 570. See also Vitamins, B
Pemphigus; case for diagnosis, 142
epidermolysis bullosa; recently described variant, *91
erythematosus (Senear-Usher type), 721
experimental studies on question of cause, 264
familial benign chronic or bullous dyskeratosis, 730
foliaceus; patient treated with unusual amount of acetarsone, *691
histologic findings and Herzberg's stain for virus in, 264
ocular, with scarring of skin and mucous membranes, *37
or dermatitis herpetiformis, 415
Pemphigus—Continued
or lupus erythematosus, 270
vulgaris, 592, 720
vulgaris; study of blood picture, *772
Penicillin; dermatitis venenata due to penicillin-containing ointment, 582
levels in serum and some body fluids during systemic and local therapy, 551
reaction, 549
reaction simulating serum sickness, 261
reactions in treatment of syphilis, *385
Therapy: See also Eyelids; Granuloma inguinale; Pyoderma; Seborrhea; Skin, diseases; Sycosis; Syphilis; Ulcers; Urticaria; etc.
therapy, topical; principles of local therapy with penicillin ointment mixtures, *793
Penis; dermatitis venenata or erythroplasia, 845
erythroplasia (Bowen's disease of mucous membranes), 265
Pensky, N.: Sarcoidosis, 421
Periadenitis: See under Lymph Nodes
Perlman, H. H.: Trichotillomania, 859
Permanent Waving: See Cosmetics
Perry, D. J.: Role of food allergy in eczematoid dermatitis, *493
Perspiration: See under Sweat Glands
Phalanges: See Fingers and Toes
Phlebectasia: See Varicose Veins
Philpott, O. S.: Sulfonamide psoriasiform dermatitis, *525
Photosensitization: See under Light
Phthirus Pubis: See Pediculosis
Phthisis: See Tuberculosis, pulmonary
Physicians: See also Obituaries; etc.
account of stock, 833
Pigmentation: See also Addison's Disease; Melanin; Nevi; Schamberg's Disease; etc.
acanthosis nigricans, 291
arsenical, and keratoses; psoriasis; squamous cell epithelioma of finger with metastasis to axillary lymph nodes, 294
dermatosis, progressive pigmentary, 297
following application of iron salts; report of case in which it was not permanent, *692
idiopathic atrophy of skin; case for diagnosis, 737
idiopathic multiple pigmented sarcoma of Kaposi, 575
lupus erythematosus or chloasma, 426
melanodermatitis (occupational), 562
parapsoriasis with pigmentation or urticaria pigmentosa, 429
pinta-like lesions among natives of Guam, 836
with dyskeratosis congenita, dystrophia unguium and leukoplakia oris; patient with evidence suggestive of Addison's disease, *242
Pili Torti: See Hair, abnormalities
Pillsbury, D. M.: Case for diagnosis, 302
Experiences in military dermatology; their interpretation in plans for improved general medical care, *441
Piñeyro, R.: Nerve lesions of leprosy, *783
Pinta, 288
pinta-like lesions among natives of Guam (peladang), 836
White: See Vitiligo
Pituitary Body; treatment of post-traumatic Simmonds' disease with methyl testosterone linguets, 834
Pityriasis Lichenoides: See Parapsoriasis
rosea, 154
rubra pilaris, 709, 725
rubra pilaris and vitamin A, 401
rubra pilaris with exfoliation, 141
Plants: See under names of plants, as Rhus; etc.
Plasmodium: See Malaria
Pneumococci; effect of sodium bicarbonate on therapeutic effectiveness of sulfadiazine in mice, 697
Poikiloderma atrophicans vasculare; case for diagnosis, 588, 706
atrophicans vasculare (Jacobi), 590
Poison Ivy: See Rhus
Poison Oak: See Rhus
Poisons and Poisoning: See under names of poisonous substances

Polycythemia or poikiloderma atrophicans vasculare, 588
Polymyositis: See Dermatomyositis
Poradenitis: See Lymphogranuloma Venereum
Porokeratosis: See Keratosis
Poryphyria: See Porphyrin and Porphyrin Compounds
Porphyrin and Porphyrin Compounds; acute porphyria; clinical and pathologic observations, 398
Postgraduate Education: See Education
Pratt, A. G.: Hemangioma, 304
Pregnancy; chronic latent oral moniliasis (thrush); report of case of 12 years' duration in which disease was resistant to treatment, *85
congenital glaucoma following maternal rubella, 549
herpes gestationis, 715
Moeller's glossitis; case with remission during pregnancy, *463
penicillin in prevention of prenatal syphilis, 699
Price, H.: Lipoidosis cutis et mucosae; report of case, *42
Prickly Heat: See Miliaria
Printz, D. R.: Dermatosis, progressive pigmentary, 297
Larva migrans, 296
Myoblastoma, 297
Prognosis: See under names of diseases
Promizole: See Tuberculosis
Propamidine: See Amidines
Propionic Acids: Se Ringworm
Proteinosis, Lipid: See Lipoids, metabolism
Proteins, deficiency; its relationship to palmar erythema, 398
possible benefit from protein hydrolysates for exfoliative dermatitis, *397
Prurigo nodularis, 423
Pruritus; benadryl in dermatologic therapy, *101
lichen planus with involvement of palms, 295
lichenoid dermatitis (New Guinea type), 576
Pseudopelade: See Alopecia, cicatrisata
Pseudoxanthoma elasticum, 285
Psoriasis and Streptococcus faecalis; possible interrelation, 119
arsenical pigmentation and keratoses; squamous cell epithelioma of finger with metastasis to axillary lymph nodes, 294
basal cell epithelioma in psoriatic patch, *375
case for diagnosis, 570
granuloma annulare or sarcoid, 151
of palms, 134
or dermatitis medicamentosa, 412
or ichthyosis hystrix, 268
or onychomycosis, 850
sulfonamide psoriasiform dermatitis, *525
superficial basal cell epitheliomas on, 125
Psychobiology: See Mind, body and mind
Psychoneurosis: See Neuroses and Psychoneuroses
Psychoses: See Neuroses and Psychoneuroses
Purple X bulb in diagnosis of fungous diseases of scalp, *396
Purpura annularis telangiectodes, 847
purpuric eruption of lower extremities resembling Schamberg's disease; case for diagnosis, 148
Pyoderma gangrenosum, 714
Kaposi's varicelliform eruption, *327
topical use of penicillin in treatment of, *630
treatment with interface active solution of tyrothricin, 260
Pyribenzamine, new antihistaminic compound; clinical use in certain cutaneous disorders, *309

Quinacrine: See Acridine Dyes

Races: See Negroes; etc.
Radiodermatitis: See Roentgen Rays
Radium, Therapy: See under names of various diseases, as Lips, cancer; etc.
Radon: See Roentgen Rays
Rat Mite: See Mites
Rattner, H.: Dermatomyositis; case for diagnosis, 570
Moeller's glossitis; case with remission during pregnancy, *463
Mycosis fungoides, 562
Rausch, N. G.: Clinical use of new antihistaminic compound (pyribenzamine) in certain cutaneous disorders, *309
Ravitz, S. E.: Neural leprosy; case for diagnosis, 569
Raynaud's Disease; venospasm; its part in producing clinical picture of Raynaud's disease, 399
von Recklinghausen's Disease: See Neurofibromatosis
Reconditioning: See Rehabilitation
Rees, R. B.: Bullous dyskeratosis (familial benign chronic pemphigus), 730
Idiopathic multiple pigmented sarcoma of Kaposi, 575
Rehabilitation of patients suffering from skin disease, 263
Reiss, F.: Basal squamous cell epithelioma associated with leukemia, *507
Reticuloendothelial System; eosinophilic granuloma; theoretic and practical considerations based on study of case, *176
identification of inhibitory factor of reticuloendothelial immune serum (REIS) in globulin fraction, 261
reticuloendotheliosis or mycosis fungoides, 286
reticulum, or lattice, fibers; further studies, *478
skin and reticular tissue, 552
Reticuloendotheliosis: See Reticuloendothelial System
Reticulosis: See Reticuloendothelial System
Reticulum: See Tissues, connective
Rheumatic Fever, skin lesions of, 262
Rhinoscleroma, 733
Rhus; observations and data on prevention of poison oak dermatitis, 837
pigmentation following application of iron salts; report of case in which it was not permanent, *692
studies on poison ivy and other dermatitis producing plants wherein active, resinous principles are suspended in aqueous solution, 399
Rickettsial Diseases: See Rocky Mountain Spotted Fever
Riehl's Disease: See Melanin
Rifles: See Guns
Ringworm: See also Favus; Mycosis, cutaneous; Tinea; Trichophytosis; etc.
tinea capitis due to Microsporon audouini (3 cases), 147
tinea capitis in southeastern Tennessee, *258
undecylenic and propionic acids in prevention and treatment of dermatophytosis, *391
use of Purple X bulb in diagnosis of fungous diseases of scalp, *396
Ritter's Disease: See Dermatitis, exfoliative
Robinson, S. S.: Acanthosis nigricans juvenilis associated with obesity; report of case with observations on endocrine dysfunction in benign acanthosis nigricans, *749
Chronic latent oral moniliasis (thrush); report of case of 12 years' duration in which disease was resistant to treatment, *85
Rocky Mountain Spotted Fever, 550
Rodin, H. H.: Mycosis fungoides, 562
Roentgen rays, dermatitis, superficial epithelioma, Bowen's disease or neurodermatitis, 851
dermatitis treated with radon ointment, 581
radiodermatitis, 585
radiodermatitis of dorsal surface of hands, 587
Therapy: See under names of organs, regions and diseases, as Bones; Mycosis fungoides; Epithelioma; Sarcoma; etc.
Ronchese, F.: Dermatitis herpetiformis or pemphigus, 415
Rosacea: See Acne rosacea

Rosen, I.: Neurodermatitis—hypertrophic or tumid type; case for diagnosis, 708
Poikiloderma vasculare atrophicans; case for diagnosis, 706
Rothman, S.: Acanthosis nigricans, juvenile type, 139
Calcinosis, generalized, 141
Disseminated subacute lupus erythematosus (?), 565
Erythema induratum (Bazin), 560
Facial hemiatrophy, 135
Heat and emotional urticaria, 566
Juxta-articular nodes, origin undetermined, 129
Lichen nitidus, 567
Linear scleroderma with spina bifida, 130
Lipid proteinosis, 127
Rat mite dermatitis, 138
Xanthomatous biliary cirrhosis with flat xanthomas of eyelids, 556
Rubella; congenital glaucoma following maternal rubella, 549
Rubrophen: See Tuberculids
Rule, A. M.: Penicillin in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin in single and multiple doses in isotonic solution of sodium chloride and peanut oil-beeswax by intramuscular injection, *741
Rulison, R. H.: Glossitis rhomboidea mediana, 728

Sachs, W.: Epidermolysis bullosa; recently described variant, *91
Sáenz, B.: Relapsing syphilids of genitalia; persistence of lesions 7 months after serologic reversion, *650
Sagher, F.: Leishmania vaccine test in leishmaniasis of skin (Oriental sore); quantitative experiments, *658
Sailors: See Naval Medicine
Salicylazosulfapyridine: See Sulfonamides
Salvarsan: See Arsphenamines
Samitz, M. H.: Case of Bowen's disease, 861
Sanarelli-Shwartzman Phenomenon: See Shwartzman Phenomenon
Sarcoidosis, 421
Boeck's sarcoid, 153
cutaneous manifestations of lymphogranulomatosis benigna (Schaumann), 123
granuloma annulare, psoriasis or sarcoid, 151
of skin, 711
relationship of Boeck's sarcoid and tuberculosis; report of case in which tuberculosis of lymph nodes was associated with features highly suggestive of sarcoid, 399
sarcoid; case for diagnosis, 723
sarcoid or basal cell epithelioma, 734
sarcoid or leprosy, 589
Spiegler-Fendt sarcoid or lupus erythematosus, 736
Sarcoma: See also Cancer; Fibrosarcoma; Lymphosarcoma; Tumors; etc.
idiopathic multiple hemorrhagic (Kaposi), 564
idiopathic multiple pigmented, of Kaposi, 575
Kaposi's; case for diagnosis, 420
multiple idiopathic hemorrhagic, or hemangioendothelioblastoma, 410
mycosis fungoides and similar conditions in Negro, *111
Saunders, T. S.: Clinical experience with ointment of synthetic coal tar, *683
Scabies and pediculosis treated with benzyl benzoate, DDT and benzocaine emulsion, 835
combination treatment for lice and scabies, 835
diagnosis of infestation with "Sarcoptes scabiei" var. "hominis," 838
during war; treatment with benzyl benzoate, *455
epidemiology with attention to its relationship to venereal disease, 123
norvegica in native of East Africa, 839
or leukemid, 595
or parasitic infection, 597
Scalp; cutis verticis gyrata, 146
Diseases: See also under names of diseases, as Favus; Ringworm; Seborrhea; etc.
diseases; use of Purple X bulb in diagnosis of fungous diseases, *396
lupus erythematosus of, 143
tinea capitis due to Microsporon audouini (3 cases), 147
Scars: See Cicatrix
Schamberg's Disease; purpuric eruption of lower extremities resembling Schamberg's disease; case for diagnosis, 148
Schaumann's Disease: See Sarcoidosis
Scheer, M.: Syringoma, 843
Schmidt, O. E. L.: Dermatitis venenata due to penicillin-containing ointment, 582
Unilateral ulceration of mouth (tuberculosis orificialis?), probably with miliary and ileocecal involvement, 580
Schorr, H. C.: Multiple superficial epitheliomatosis, 134
Subacute disseminated lupus erythematosus, 136
Tuberculosis verrucosa cutis and tuberculosis colliquativa, 131
Unexplained fluorescence phenomenon, 564
Schwartz, L.: Dermatitis from glass fabrics, *258
Scleredema: See Scleroderma
Sclerema: See Scleroderma
Scleroderma, generalized progressive, associated with changes in lungs, larynx and esophagus, 269
linear, with spina bifida, 130
localized (morphea) or nevus linearis, 716
morphea-like and basal cell epithelioma of face cured by roentgen ray therapy, 585
or scleredema adultorum, 705
progressive, of skin with cystic sclerodermal changes of lungs, *1
sclerema adiposum neonatorum of both internal and external adipose tissue, 399
with involvement of viscera; report of case, 552
Scleroma: See Rhinoscleroma
Scrofula: See Tuberculosis
Scrofuloderma: See Tuberculosis
Scrotum, angiomas of, 548
Sebaceous Glands; calcified sebaceous cysts; lupus erythematosus of face, 860
development from intralobular ducts of parotid gland, 117
sebaceous secretion and denervation, 404
treatment of infected sebaceous cysts, 838
Seborrhea; dermatitis seborrheica, 717
Secretions, Internal: See Endocrine Glands
Senear, F. E.: Case for diagnosis, 138
Lymphoblastoma, 140
Senear-Usher Syndrome: See Pemphigus
Sensitization: See Anaphylaxis and Allergy; Light
Septum, Nasal: See under Nose
Serodiagnosis: See under names of reactions, as Wassermann Reaction; and under names of conditions, as Syphilis, serodiagnosis; etc.
Serum: See also Blood
antireticular cytotoxic, in chronic skin ulcers, 116
Settle, E. B.: Lipoidosis cutis et mucosae; report of case, *42
Shafer, J. C.: Treatment of early acquired syphilis with 600,000 units of sodium penicillin, *644
Shaffer, B.: Parasitic infection or scabies, 597
Shapiro, A. L.: Acanthosis nigricans, juvenile type, 139
Erythema induratum (Bazin), 560
Shaw, C.: Tinea capitis in southeastern Tennessee, *258
Shock, Anaphylactic: See Anaphylaxis and Allergy
Shoes: See Leather
Shwartzman Phenomenon; anaphylactoid (Sanarelli-Shwartzman) reaction following therapeutic antityphoid injections, 262
Sickiemia: See Anemia, sickle cell
Silvers, S. H.: Tinea barbae, 422
Simmonds' Disease: See Pituitary Body
Skeleton: See Bones

Skin: See also Dermatology
Abnormalities: See also Atrophy; Pigmentation; etc.
abnormalities; atypical chondrodystrophia of type Morquio associated with follicular atrophoderma, 266
and reticular tissue, 552
Atrophy: See Atrophy
Blood Supply: See Capillaries
Cancer: See Cancer; Epithelioma; Sarcoma; etc.
cutaneous diphtheria, 837
cutaneous manifestations of lymphogranulomatosis benigna (Schaumann), 123
cutaneous torulosis in patient with Hodgkin's disease, 738
Diphtheria: See under Diphtheria
Diseases: See also Dermatitis; and under names of diseases, as Eczema; Herpes; Mycosis; etc.; and under names of plants and drugs, as Penicillin; Rhus; etc.
diseases; benadryl in dermatologic therapy, *101
diseases; chief advances in dermatologic diagnosis and treatment occurring during war, *453
diseases; clinical experience with ointment of synthetic coal tar, *683
diseases; clinical use of new antihistaminic compound (pyribenzamine) in certain cutaneous disorders, *309
diseases; cutaneous diphtheria and tropical ulcers, *360
diseases; deficiencies in available methods of dermatologic therapy during war, *456
diseases; dermatologic problems in staging area station hospital, *322
diseases; dermatosis, progressive pigmentary, 297
diseases; experiences in military dermatology; their interpretation in plans for improved general medical care, *441
diseases; incidence in Army, *442
diseases; necrobiosis lipoidica diabeticorum, 427, 428
diseases; planning and investigations to prevent and cure diseases of skin in Army, *445
diseases, prevention and treatment during war [DDT and penicillin], *455
diseases; psychosomatic factors in dermatoses; critical analysis of diagnostic methods of approach, *601
diseases, rehabilitation of patients suffering from, 263
diseases; reticulum, or lattice, fibers; further studies, *478
diseases, role of vitamins in pathogenesis and treatment of, 699
diseases; some newer bases for use in cutaneous therapy, 260
diseases; topical penicillin therapy; principles of local therapy with penicillin ointment mixtures, *793
diseases; topical treatment with penicillin ointment, *52
diseases; unusual dermatosis simulating lichen planus and lichen corneus hypertrophicus; report of 6 cases, *12
effects of glycerite of hydrogen peroxide on infections of skin and mucous membranes, *801
eosinophilic granuloma of bone with cutaneous manifestations; report of case, *810
eosinophilic granuloma of; its relation to erythema elevatum diutinum and eosinophilic granuloma of bone; report of case, *194
eosinophilic granuloma; theoretic and practical considerations based on study of case, *176
"eosinophilic granulomas" of, *155
epithelial symptoms caused by various deficiencies, 555
future of B. P. ointments, 401
granulomatous Hodgkin's disease with extreme eosinophilia (eosinophilic granuloma of skin?), *212
Hemorrhage: See Purpura
Hodgkin's disease without demonstrable systemic involvement, 594
ichthyosiform changes associated with internal diseases, *28
Skin—Continued
Idiosyncrasy: See Anaphylaxis and Allergy; Dermatitis, venenata; etc.
Inflammation: See Dermatitis
lesions during course of ulcerative colitis, 121
lesions of rheumatic fever, 262
lipoidosis cutis et mucosae; report of case, *42
normal and hypersensitive; effect of turpentine oil, 703
Pigmentation: See under Pigmentation; Urticaria
primary lichen amyloidosis; report of necropsy, *251
protective coatings for prevention of sunburn, 118
Reactions: See Anaphylaxis and Allergy
sarcoidosis of, 711
scientific principles in design and choice of ointment bases, 553
self disinfection of; short review and some original observations, 552
sensitivity due to atabrine, 550
syphilis (primary, recurrent), 718
tertiary syphilis of, 413
Tuberculosis: See Tuberculids; Tuberculosis
Tumors: See under Tumors
Ulcers: See under Ulcers
Skolnik, E. A.: Psoriasis of palms, 134
Skull: See Cranium
Smallpox; generalized vaccinia, 120
Smith, D. C.: Treatment of early acquired syphilis with 600,000 units of sodium penicillin, *644
Social Conditions: See under Venereal Diseases
Societies; Rocky Mountain dermatologic society formed, 831
Society for Investigative Dermatology, 432

Society Transactions:
Brooklyn Dermatological Society, 421, 720
Chicago Dermatological Society, 127, 556
Cleveland Dermatological Society, 277
Los Angeles Dermatological Society, 124, 427
Manhattan Dermatologic Society, 705
Metropolitan Dermatological Society, 150, 416, 844
Minnesota Dermatological Society, 143
New England Dermatological Society, 405, 711
New York Academy of Medicine, Section of Dermatology and Syphilis, 425, 840
New York Dermatological Society, 268, 582, 723
Philadelphia Dermatological Society, 299, 591, 854
San Francisco Dermatological Society, 572, 728

Soda, W.: Case for diagnosis, 420
Sodium, bicarbonate; effect on therapeutic effectiveness of sulfadiazine in mice, 697
chloride; penicillin in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin in single and multiple doses in isotonic solution of sodium chloride and peanut oil-beeswax by intramuscular injection, *741
Gold Thiosulfate: See Gold and Gold Compounds
Soldiers: See Armed Forces Personnel; Aviation and Aviators; Military Medicine; etc.
Spiegler-Fendt Sarcoid: See Sarcoidosis
Spina Bifida with linear scleroderma, 130
Spirochaeta Pallida: See Syphilis
Sporotrichosis or secondary syphilis [treated], 727
papulopustular verrucous, simulating blastomycosis, 290
Spotted Fever: See Rocky Mountain Spotted Fever; Typhus
Stains and Staining; histologic findings and Herzberg's stain for virus in pemphigus, 264
reticulum, or lattice, fibers; further studies, *478
Stevens-Johnson Syndrome: See Erythema multiforme
Steves, R. J.: Kaposi's varicelliform eruption, *327
Still's Disease: See Arthritis, rheumatoid

Stokes, J. H.: Erich Urbach, 545
Stomatitis, aphthous, or periadenitis mucosa necrotica recurrens, 709
due to ingested medication; case for diagnosis, 126
Stevens-Johnson syndrome (eruptive fever with stomatitis and conjunctivitis), 832
Strauss, M. J.: Pigmentation following application of iron salts; report of case in which it was not permanent, *692
Strawberry Nevi: See Angioma
Streptococci faecalis and psoriasis; possible interrelation, 119
Streptomycin: See Bacteria; Tuberculosis
Striae distensae, 559
Stubenrauch, C. H., Jr.: Case for diagnosis, 138
Sudoriparous Glands: See under Sweat Glands
Sulfadiazine: See Mycetoma; Sulfonamides
Sulfapyridine: See Dermatitis herpetiformis; Sulfonamides
Sulfonamides; dermatitis medicamentosa; case for diagnosis, 414
effect of sodium bicarbonate on therapeutic effectiveness of sulfadiazine in mice, 697
erythema multiforme bullosum and dermatitis medicamentosa [sulfonamide compounds], 852
medication, erythema multiforme bullosum due to, 853
psoriasiform dermatitis, *525
psoriasis or dermatitis medicamentosa, 412
Therapy: See Dermatitis herpetiformis; Furunculosis; Mycetoma; etc.
Sulfones: See Tuberculosis
Sulzberger, M. B.: Undecylenic and propionic acids in prevention and treatment of dermatophytosis, *391
Sunburn: See Light
Sunlight: See under Light
Suprarenal Preparations: See Adrenal Preparations
Suprarenals: See Adrenals
Suskind, R. R.: Topical penicillin therapy; principles of local therapy with penicillin ointment mixtures, *793
Sutton, R. L., Jr.: Angiomas of scrotum, 548
Sutton's Disease: See Vitiligo
Sweat Glands; acne conglobata, 284
hidradenitis suppurativa, 713
syringoma, 843
treatment of infected sebaceous cysts, 838
tropical anhidrotic asthenia (thermogenic anhidrosis) and its relationship to prickly heat, 260
Sweeney, A. R.: Acne conglobata, 284
Sweitzer, S. E.: Alopecia areata in infants, 143
Atrophoderma hypoestrogenicum, 148
Cavernous hemangioma of lip, 145
Dermatitis medicamentosa due to gold sodium thiosulfate, 147
Gumma of nose and upper lip, 145
Gumma of testicle; case for diagnosis, 144
Lupus erythematosus of scalp, 143
Purpuric eruption of lower extremities resembling Schamberg's disease; case for diagnosis, 148
Tinea capitis due to Microsporon audouini (3 cases), 147
Sycosis, chronic coccogenous, treated locally with penicillin, 573
lupoid, 274
Synovial Membrane; longitudinal grooving of nails caused by synovial lesions, *828
Syphilids, annular macular, 300
relapsing, of genitalia; persistence of lesions 7 months after serologic reversion, *650
Syphilis: See also Neurosyphilis; Syphilids; Venereal Diseases; and under names of organs, regions and diseases, as Eyes; Meninges; etc.
acute syphilitic bilateral total ophthalmoplegia, *686
agranulocytosis; report of 12 cases in which it followed intensive arsenotherapy for syphilis, *57
bismuth in treatment, 116
congenital, and hemolytic disease in siblings, 263
Diagnosis: See Syphilis, serodiagnosis
Syphilis—Continued
dichlormapharsen in treatment, 836
early acquired; treatment with 600,000 units of sodium penicillin, *644
early; out-patient treatment with penicillin, 701
early; penicillin therapy in 14,000 patients; follow-up examination of 792 patients 6 or more months after treatment, 698
early; relapse following penicillin therapy, 572
early tertiary, 150
effect of penicillin in experimental rabbit syphilis, 119
experimental, of rabbits; penicillin in treatment; therapeutic activity of penicillin in single and multiple doses in isotonic solution of sodium chloride and peanut oil-beeswax by intramuscular injection, *741
Hereditary: See Syphilis, congenital
of skin (primary, recurrent), 718
postarsphenamine vitiligo, 272
prenatal, penicillin in prevention of, 699
problem of reinoculation of human beings with Spirocheta pallida, 698
pustular, 859
reactions in treatment with penicillin, *385
secondary [treated] or sporotrichosis, 727
serodiagnosis; cardiolipin-lecithin antigen; recent development toward single standard test of blood for syphilis, *514
some obscure and paradoxical problems of, 700
syphilitic glossitis; case for diagnosis, 407
syphilitic keratosis, 578
tertiary, frambesiform, 840
tertiary; gumma of nose and upper lip, 145
tertiary; gumma of testicle; case for diagnosis, 144
tertiary, of skin, 413
tertiary, simulating lupus annularis of cervical region, 554
toxic effects of arsenical compounds as administered in United States Navy in 1944, with reference to arsenical dermatitis, 262
tuberculosis orificialis; case for diagnosis, 409
visit to leper colony, 702
Syphiloid; "eosinophilic granulomas" of skin, *155
Syringocystadenoma, 420
Syringoma, 843
Syringomyelia; perforating ulcer of foot in 2 sisters, 430

Tar; clinical experience with ointment of synthetic coal tar, *683
Tasker, S.: Acanthosis nigricans juvenilis associated with obesity; report of case with observations on endocrine dysfunction in benign acanthosis nigricans, *749
Chronic latent oral moniliasis (thrush); report of case of 12 years' duration in which disease was resistant to treatment, *85
Tavs, L. E.: Urticaria pigmentosa with bullae, 558
Teaching: See Education
Templeton, H. J.: Papular urticaria or dermatitis herpetiformis, 731
Spiegler-Fendt sarcoid or lupus erythematosus, 736
Terminology: See Nomenclature
Testes; gumma of testicle; case for diagnosis, 144
penicillin in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin in single and multiple doses in isotonic solution of sodium chloride and peanut oil-beeswax by intramuscular injection, *741
Testosterone: See Androgens
Thiamine: See Vitamins, B
Thigh: See Legs
Throat: See Larynx
Thromboangiitis obliterans, use of trichophytin in, *512
Thrush: See Moniliasis
Thumbs: See under Fingers and Toes

Thurmon, F. M.: Effects of glycerite of hydrogen peroxide on infections of skin and mucous membranes, *801
Psoriasis or dermatitis medicamentosa, 412
Thyroid: See Parathyroid
Tiant, F. R.: Nerve lesions of leprosy, *783
Tick Fevers: See Rocky Mountain Spotted Fever
Tinea: See also Ringworm
barbae, 422
Capitis: See Ringworm
corporis (glabrosa); dermatophytosis of hands and feet, 848
Decalvans: See Alopecia areata
Favosa: See Favus
nigra, *67
Tissue: See also Cells
Adipose: See Fat
birefringence in, 834
connective; reticulum, or lattice, fibers; further studies, *478
connective; scleroderma with involvement of viscera; report of case, 552
skin and reticular tissue, 552
Staining: See Stains and Staining
Toes: See Fingers and Toes
Nails: See Nails
Tomaszewski, W.: Ichthyosiform changes of skin associated with internal diseases, *28
Tongue, angiomas associated with angiomas of scrotum, 548
glossitis rhomboidea mediana, 727
lichen planus, 153
Moeller's glossitis; case with remission during pregnancy, *463
myoblastoma, 297
syphilitic glossitis; case for diagnosis, 407
Torrey, F. A.: Cutaneous torulosis in patient with Hodgkin's disease, 738
Hodgkin's disease complicated by squamous cell epithelioma of neck, 574
Lymphoblastoma, 735
Torula; cutaneous torulosis in patient with Hodgkin's disease, 738
Toxicoderma: See Dermatitis venenata; Drugs, eruptions
Trachea; search for virus-inactivating substances among microorganisms, 119
Traub, E. F.: Granuloma annulare, generalized, 583
Larva migrans, 728
Sarcoid; case for diagnosis, 723
Trichoderma: See Fungi
Trichoepithelioma, 726
Trichofolliculoma: See Hair
Trichophytid: See Trichophytosis
Trichophytin: See Thromboangiitis
Trichophyton camerounense, cause of dermatophytosis of face, *337
Trichophytosis; kerions, 572
use of trichophytin in thromboangiitis obliterans, *512
Trichotillomania, 859
Tropical Medicine: See also under names of tropical diseases, as Leishmaniasis; Ulcers, tropical; etc.
atypical lichen planus tropicalis, *535
cutaneous diphtheria occurring during war, *454
lichenoid dermatitis, 835
prickly heat, 554
topical use of penicillin in treatment of pyoderma, *630
tropical anhidrotic asthenia (thermogenic anhidrosis) and its relationship to prickly heat, 260
Tropics: See Tropical Medicine; and under names of diseases, as Diphtheria; Miliaria
Tubercle Bacilli: See Tuberculosis
Tuberculids: See also under Tuberculosis
rubrophen in cutaneous tuberculosis, 703
Tuberculosis: See also Tuberculids; and under names of diseases, organs and regions, as Lymph Nodes; etc.
allergy, development of, 702
and Boeck's sarcoid, relationship of; report of case in which tuberculosis of lymph nodes was associated with features highly suggestive of sarcoid, 399
colliquativa and tuberculosis verrucosa cutis, 131
Tuberculosis—Continued
cutaneous; treatment of various types with promizole and streptomycin; preliminary report, *222
cutis or Bowen's disease, 418
cutis orificialis with underlying pulmonary tuberculosis, 571
nerve lesions of leprosy, *783
of skin, 587
or lichen nitidus, 567
orificialis; case for diagnosis, 409
orificialis; unilateral ulceration of mouth (tuberculosis orificialis?), probably with miliary and ileocecal involvement, 580
pulmonary; tuberculosis cutis orificialis with underlying pulmonary tuberculosis, 571
scrofuloderma, 132
verrucosa cutis and tuberculosis colliquativa, 131
visit to leper colony, 702
Tumors: See also Angioma; Cancer; Dermatofibroma; Epithelioma; Fibrosarcoma; Granuloma; Hemangioma; Lymphoblastoma; Lymphosarcoma; Melanoma; Myoblastoma; Myoma; Rhinoscleroma; Sarcoma; Syringoma; and under names of organs and regions, as Nerves; etc.
cutaneous horn, 282
new type of granulomatosis with generalized tumors simulating mycosis fungoides with fatal outcome, 265
Turpentine oil; effect on normal and hypersensitive skin, 703
Twins; multiple keloids in twin sisters, 426
Typhoid; anaphylactoid (Sanarelli-Shwartzman) reaction following therapeutic antityphoid injections, 262
Typhus; allergic reaction following typhus fever vaccine and yellow fever vaccine due to egg yolk sensitivity, 400
Tyrothricin: See Pyoderma

Ulcers: See also under names of organs and regions
acute pyogenic, factitial or anaerobic, 301
antireticular cytotoxic serum in chronic skin ulcers, 116
cause of phagedenic soft chancre, 267
perforating, of foot in 2 sisters, 430
sickle cell anemia in white patients with ulcers of ankles; report of 2 cases, 833
trophic, and inflammation in denervated areas, 403
Tropical: See also Leishmaniasis; etc.
tropical, and cutaneous diphtheria, *360
tropical, in Guatemala, 117
tropical; initial treatment, 263
tuberculosis cutis orificialis with underlying pulmonary tuberculosis, 571
unilateral ulceration of mouth (tuberculosis orificialis?), probably with miliary and ileocecal involvement, 580
Varicose: See Varicose Veins
Ultraviolet Rays: See under Light
Therapy: See under names of organs, regions and diseases
Undecylenic Acid: See Moniliasis; Ringworm
Urea; effect of urea, urethane and other carbamates on bacterial growth, 119
Urethane: See Ethyl Carbamates
Urticaria; benadryl in dermatologic therapy, *101
clinical use of new antihistaminic compound (pyribenzamine) in certain cutaneous disorders, *309
emotional, and heat, 566
giant, with lymphedema, 416
papular, or dermatitis herpetiformis, 731
pigmentosa (nodular type), 280
pigmentosa of peculiar, livedo-racemosa-like design, 266
pigmentosa or parapsoriasis with pigmentation, 429
pigmentosa with bullae, 558
reaction to penicillin simulating serum sickness, 261
solare (4000-5000A), 836
solaris; studies in hypersensitivity to light, 836

Urticaria—Continued
use of histamine antagonist, beta-dimethylaminethyl benzhydryl ether hydrochloride, in allergic disease, 832
Usher-Senear Syndrome: See Pemphigus

Vaccine Therapy: See Furunculosis; Leishmaniasis; Typhoid; Typhus; Yellow Fever; etc.
Vaccinia: See Smallpox
Vagina; chronic latent oral moniliasis (thrush); report of case of 12 years' duration in which disease was resistant to treatment, *85
Varicella: See Chickenpox
Varicose Veins; congenital absence of valves in veins as cause of varicosities, *639
Variola: See Smallpox
Vaselinoderma, verrucosum; case for diagnosis, 131
Vasomotor System: See also Arteries; Capillaries; Veins
allergic reaction following typhus fever vaccine and yellow fever vaccine due to egg yolk sensitivity, 400
angioneurotic edema, 591
mechanism of axonal vasodilation, 403
Veins: See also Vasomotor System; etc.
congenital absence of valves in veins as cause of varicosities, *639
Varicose: See Varicose Veins
venospasm; its part in producing clinical picture of Raynaud's disease, 399
Venereal Diseases: See also Chancroid; Gonorrhea; Neurosyphilis; Syphilis; etc.
epidemiology of scabies with attention to its relationship to, 123
in Army Air Forces in continental United States, 1942-1944, 697
relation of dermatology and venereology, *452
Verruca, confluent eruption of verrucae planae of hands, forearms and neck, simulating epidermodysplasia verruciformis, associated, however, with verrucae vulgaris, 267
epidermodysplasia verruciformis, 727, 845
epidermodysplasia verruciformis [inoculation test], 534
epidermodysplasia verruciformis or chronic myeloid leukemia, 280
keratosis palmaris et plantaris (epidermodysplasia verruciformis?), 856
leishmaniasis verrucosa of face, *358
papulopustular verrucous sporotrichosis simulating blastomycosis, 290
Tuberculosis: See under Tuberculosis
Vesication, bullous dyskeratosis (familial benign chronic pemphigus), 730
lichen sclerosus et atrophicus with bullous lesions and extensive involvement; report of case, *433
pemphigus vulgaris, 720
urticaria pigmentosa with bullae, 558
Viruses: See also Herpes simplex; Stains and Staining
search for virus-inactivating substances among microorganisms, 119
Viscera, scleroderma with involvement of; report of case, 552
Vitamins; role in pathogenesis and treatment of skin diseases, 699
A and pityriasis rubra pilaris, 401
A; case for diagnosis, 138
A; ichthyosiform changes of skin associated with internal diseases, *28
A; juvenile acanthosis nigricans and ichthyosis, 411
A treatment of acne vulgaris, *355
B: See also Pellagra
B; epithelial symptoms caused by various deficiencies, 555
Vitiligo, generalized; alopecia of undetermined cause, 425
leukoderma acquisitum centrifugum, 429
leukoderma acquisitum centrifugum (Sutton) and reproduction of presentation of similar cutaneous changes on panel of altar of Isenheim, 266
postarsphenamine, 272
Vulvovaginitis, monilial; undecylenic acid in treatment, *113

Walzer, A.: Prurigo nodularis, 423
Pseudopelade, 424
War: See Aviation and Aviators; Military Medicine; Naval Medicine; etc.
Warts: See Verruca
Wassermann Reaction: See also under Syphilis
falsely positive Wassermann and Kahn reactions in infective hepatitis, 701
Way, S. C.: Reticulum, or lattice, fibers; further studies, *478
Wearing Apparel: See Clothing; Leather
Weber-Christian Disease: See Panniculitis
Weichselbaum, P. K.: Lymphoblastoma, 140
Weidman, F. D.: Annular, macular syphilid, 300
"Eosinophilic granulomas" of skin, *155
Granulomatous Hodgkin's disease of skin with extreme eosinophilia (eosinophilic granuloma of skin?), *212
Iodide dermatitis, 305
Leukemid or scabies, 595
Westcott, R. J.: Elephantiasis neuromatosa; manifestation of von Recklinghausen's disease, *233
Wheal: See Urticaria
White, C. J.: Neural leprosy; case for diagnosis, 569
Striae distensae, 559
White Spot Disease: See Scleroderma
Winer, L. H.: Atrophoderma hypoestrogenicum, 148
Winiwarter-Buerger Disease: See Thromboangiitis obliterans
Wise, F.: Erythema annulare centrifugum, 582
Exudative discoid and lichenoid chronic dermatosis, 273
Lupoid sycosis, 274
Parapsoriasis en gouttes, 589
Poikiloderma vasculare atrophicans (Jacobi), 590
Radiodermatitis of dorsal surface of hands, 587
Tuberculosis of skin, 587
Wolf, J.: Basal cell epithelioma of forearm, 425
Lupus erythematosus or chloasma, 426
Nodular lesions of face; case for diagnosis, 842
Pityriasis rubra pilaris, 709
Wood's Light: See Fluorescence
Wounds; effect of urea, urethane and other carbamates on bacterial growth, 119
Wright, C. S.: Dermatitis herpetiformis, 854
Disseminated lupus erythematosus treated with sodium bismuth triglycollamate ("bistrimate tablets"), 862, 863
Keratotic lupus erythematosus treated with sodium bismuth triglycollamate ("bistrimate tablets"), 863
Larva migrans, 856
Pachyonychia congenita; report of 2 cases with studies on therapy, *819
Topical treatment with penicillin ointment, *52

Xanthelasma: See under Xanthoma
Xanthoma disseminatum, 406
disseminatum and tuberosum et planum, 405
eruptivum, 556
xanthomatous biliary cirrhosis with flat xanthomas of eyelids, 556
Xanthomatosis: See Xanthoma
X-Rays: See Roentgen Rays

Yaws: See Frambesia
Yellow Fever; allergic reaction following typhus fever vaccine and yellow fever vaccine due to egg yolk sensitivity, 400

Zakon, S. J.: Idiopathic multiple hemorrhagic sarcoma (Kaposi), 564
Zinc: See Mycosis
Zona: See Herpes zoster
Zugerman, I.: Angioneurotic edema, 591

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CONTENTS

PAGE

PENICILLIN IN THE TREATMENT OF EXPERIMENTAL SYPHILIS OF RABBITS: I. THE THERAPEUTIC ACTIVITY OF PENICILLIN IN SINGLE AND MULTIPLE DOSES IN ISOTONIC SOLUTION OF SODIUM CHLORIDE AND PEANUT OIL-BEESWAX BY INTRAMUSCULAR INJECTION. **John A. Kolmer, M.D., with the Technical Assistance of Anna M. Rule, Philadelphia** 741

ACANTHOSIS NIGRICANS JUVENILIS ASSOCIATED WITH OBESITY: REPORT OF A CASE, WITH OBSERVATIONS ON ENDOCRINE DYSFUNCTION IN BENIGN ACANTHOSIS NIGRICANS. **Saul S. Robinson, M.D., and Samuel Tasker, M.D., Los Angeles** 749

MADURA FOOT (MYCETOMA): FIRST REPORT FROM THE ISTHMUS OF PANAMA. **Carlos Calero M., M.D., Panamá, Republic of Panama** 761

PEMPHIGUS VULGARIS: A STUDY OF THE BLOOD PICTURE. **Arthur W. Grace, M.D., Brooklyn** 772

NERVE LESIONS OF LEPROSY. **V. Pardo-Castello, M.D.; Francisco R. Tiant, M.D., and Raul Piñeyro, M.D., Habana, Cuba** 783

TOPICAL PENICILLIN THERAPY: II. THE PRINCIPLES OF LOCAL THERAPY WITH PENICILLIN OINTMENT MIXTURES. **Leon Goldman, M.D.; Raymond R. Suskind, M.D., and Forman Friend, M.D., Cincinnati.** 793

EFFECTS OF GLYCERITE OF HYDROGEN PEROXIDE ON INFECTIONS OF THE SKIN AND MUCOUS MEMBRANES. **Francis M. Thurmon, M.D., and Ethan Allan Brown, M.D., Boston** 801

EOSINOPHILIC GRANULOMA OF BONE WITH CUTANEOUS MANIFESTATIONS: REPORT OF A CASE. **Arthur C. Curtis, M.D., and Edward P. Cawley, M.D., Ann Arbor, Mich.** 810

PACHYONYCHIA CONGENITA: REPORT OF TWO CASES, WITH STUDIES ON THERAPY. **Carroll S. Wright, M.D., and Jacques P. Guequierre, M.D., Philadelphia** 819

LONGITUDINAL GROOVING OF THE NAILS CAUSED BY SYNOVIAL LESIONS. **C. Russell Anderson, M.D., Beverly Hills, Calif.** 828

NEWS AND COMMENT 831

ABSTRACTS FROM CURRENT LITERATURE 832

SOCIETY TRANSACTIONS:

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILOLOGY 840

METROPOLITAN DERMATOLOGICAL SOCIETY 844

PHILADELPHIA DERMATOLOGICAL SOCIETY 854

BOOK REVIEWS 864

GENERAL INDEX 869